Editorial

The Need for Support of Medical Research

LARGE numbers of Japanese, Thai, Korean and other nations' students come to the United States for postgraduate study in the medical sciences. Time and money are spent on training them to be expert research workers, and it is always a pleasant surprise to see how really first class they become. After two or three years it is time to go home—and cold reality suddenly strikes. Home to what? In most cases to research facilities that are wholly inadequate and with working budgets to support a hundred investigators that would not support one investigator in the laboratories they are leaving. And this is no exaggeration. Most of these well trained young investigators will have to practice medicine a large part of the time in order to be allowed a few hours a day (often night) for research—a tremendous waste of their badly needed talents. With inadequate money, time and facilities, and often with little or no encouragement to do independent research, it is small wonder that too little research comes from these men who showed so much promise. The training operation becomes mostly sheer waste. There are at least several remedies.

The World Health Organization should lend its wisdom, prestige and administrative capacity to convince these nations of the loss they are sustaining by not supporting their research potential. Not only loss of research achievements but also the loss of their most promising young scientists to other nations willing to provide research support. Some ringing leadership from this great organization could accomplish wonders.

Some of the older leaders in medicine should be persuaded to welcome the new aggressive spirit of research in the world today, and the new attitude of the world's people towards it. Many nations that are now giving little support to medical research are providing relatively vigorous support for industrial research and development. Industry, life insurance companies and government must be persuaded that support of the life sciences is quite as important, and to some of us it seems a little more important.

Why does the pharmaceutical industry elsewhere not provide at least the sort of support that is given in the United States? Many companies have subsidiaries in foreign lands from which it is difficult, or impossible, to get their dollars out of the country because of currency restrictions. Some of these funds could be used for the full-time support of well trained young research workers to the benefit of all. Governments also have

similar blocked funds that could be put to good use.

The same can be said for the life insurance industry. While it is true that in the United States the amount they give is trivial relative to their enormous resources, still what they do is in the right direction. Since this industry is a prime beneficiary of medical research, its contribution should be much greater.

Lastly, many countries are now sufficiently prosperous so that thought should be given to appeals for money from the public. This sort of appeal has been remarkably successful for organizations such as the American Heart Association and the American Cancer Society. Since the reaction to this suggestion is usually defeatist, let us point out that the same reaction prevailed in the United States 20 years ago. It is good both for the public and for research to develop the habit of generous personal giving. Both grow in stature as a result. But science and scientists must provide the leadership and this is often hard for them to realize and accept. The movement will occur only when some dedicated scientists accept the challenge to persuade business people to join with them in an organized appeal for support from the public. We can testify from personal experiences of the heart warming response the public gives when the problem is put before it in a way that it can understand. It would be well if senior doctors visiting laboratories and medical schools in this country would also spend a portion of their time in learning how private health organizations have been organized and run. This would facilitate starting similar organizations in their own countries.

We do only half the job when we train young foreign investigators. Some way must be found to give them the badly needed opportunity to put their skills to the use of mankind. The need is urgent; time and life will not wait.

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Cerebral Sclerosis and Cerebral Circulation

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For the diagnosis of the disease called "cerebral sclerosis" there is scarcely any objective standard, and the term is vague and somewhat misleading. An attempt was made to define the conditions of cerebral sclerosis from the viewpoint of cerebral hemodynamics with N_2O method to make some clinical asset.

From the results of hemodynamic study one may diagnose the case as cerebral sclerosis when a marked decrease in CBF and $CMRO_2$, and a rise of CVR are observed. Appropriate therapeutic methods were also discussed.

IN the recent years, cerebral apoplexy has occupied the highest rank among the causes of death in Japan and the problem of cerebral sclerosis has naturally become a center of attention in medical field. Unfortunately, however, there is no reliable clinical standard for the diagnosis of cerebral sclerosis. The classification of the cerebral vascular diseases[1] which has been made in America by the committee organized by Dr. Millikan, chairman, and many other eminent neurologists, is shown in Table I. In this, mention of

Table I. Classification of Cerebrovascular Diseases

1) **Cerebral infarction**
   - thrombosis with atherosclerosis
   - cerebral embolism
   - other conditions causing cerebral infarction
   - cerebral infarction of undetermined type

2) **Transient cerebral ischemia without infarction**
   - recurrent focal cerebral ischemic attacks
   - transient cerebral ischemia with systemic hypotension
   - migraine, including migrainous hemiplegia, etc.

3) **Intracranial hemorrhage**
   - hypertensive intracerebral hemorrhage
   - ruptured saccular aneurysm
   - angioma
   - trauma
   - other causes of intracranial hemorrhage

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4) **Vascular malformations and developmental abnormalities**
   aneurysm
   angioma
   trigeminal encephalo-angiomatosis
   variations in the cerebral arteries
5) **Inflammatory disease of arteries**
   infections and infestations
   undetermined origin
6) **Vascular diseases without changes in the brain**
7) **Hypertensive encephalopathy**
8) **Dural sinus and cerebral venous thrombosis**
9) **Strokes of undetermined origin**

"cerebral sclerosis" is not made, but there is mention of a condition, called "vascular diseases without change in the brain", instead. For the diagnosis of the disease "cerebral sclerosis" there is scarcely any objective standard and the term is quite vague and somewhat misleading. However, it is inconvenient in some points to relinquish this term as it has been used commonly. The authors continue to use it as a handy way of diagnosis. Leaving the term as it is, the important thing is to understand the pathology of cerebral sclerosis which seems quite difficult with our present knowledge.

For the purpose of convenience, we have made a simple definition as follows (Fig. 1); cerebral sclerosis is the partial phenomenon of the

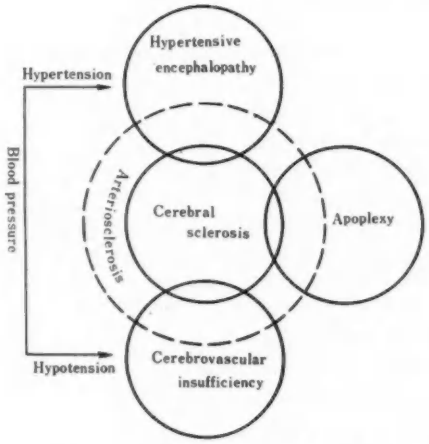


Fig. 1. Pathology of cerebral sclerosis.

sclerosis in the whole body and it does not always appear in parallel with the sclerosis of other organs. Moreover, cerebral sclerosis is relatively

sensitive to the change in environment and the influence of the whole body condition. The effect of blood pressure is especially important; by a rapid rise of blood pressure hypertensive encephalopathy is provoked and by a sudden fall of the pressure, cerebrovascular insufficiency will occur. As long as these changes remain reversible there is no danger but as in the case of progressive cerebral sclerosis sooner or later the condition progressively advances to the critical stage and results in cerebral hemorrhage or cerebral infarction.

Thus cerebral sclerosis may be regarded as an advanced stage of instability leading to the above outcome. At the Meeting of the Education Ministry in Japan, committee on arteriosclerosis, directed by Prof. Okinaka, the standard of diagnosis for cerebral sclerosis was discussed and shown to the clinician as in Table II. Cerebral selerosis—seen as an advanced

Table II. Standard of Diagnosis of Cerebral Sclerosis (June, 1960)

(1)	Age:	above 40
(2)	Symptoms:	headache, dizziness, numbness of extremities, failure of speech, increase in muscle tonus, disturbance of walk, pathologic reflex
(3)	Blood pressure:	above 160 mm.Hg systolic or above 90 mm.Hg diastolic to keep with a desirable range
(4)	Retinal finding:	above the 2nd degree of Keith-Wagener classification

Judgment

A) Almost certain
   (A-1) When conditions (1), (2), (3) and (4) are present
   (A-2) When (1) is satisfactory together with hemiplegia or clear nervous symptoms (regardless of the conditions of (2), (3) and (4))

B) Relatively certain
   (1) and (2)+(3) or (4)

C) Possible
   (1) and (2)

condition of instability—is understood as a syndrome which causes the disturbance of blood flow in the brain and as developing from arteriosclerotic changes in the cerebral vessel. From the viewpoint described above, we shall explain the hemodynamics and discuss the treatment of cerebral sclerosis according to the results of our laboratories (chiefly by N_2O method).

Hemodynamics in Cerebral Sclerosis

1. The relationship between aging and cerebral circulation.[2)]

A study of the changes in cerebral circulation and the metabolism in the aged normotensive patients and those with essential hypertension, (mean arterial blood pressure (MABP) higher than 110 mm.Hg)

revealed a decrease in cerebral blood flow (CBF) and cerebral metabolic ratio of oxygen ($CMRO_2$) and an increase in cerebral vascular resistance (CVR). The degree of these findings was more marked in the hypertensive group than that of aged normotensive group (Table III). It may be assumed that the hemodynamic change in the brain with aging is progressive.

Table III. Cerebral Hemodynamics in Each Age

Age		No. of cases	Average age	CBF	MABP	CVR	$CMRO_2$
~ 29	normotensive	48	23	61.2	94	1.61	3.52
	hypertensive	8	24	78.0	124	1.63	4.56
30 ~ 39	normotensive	44	34	56.1	93	1.69	3.40
	hypertensive	10	38	64.9	149	2.46	3.68
40 ~ 49	normotensive	18	44	53.5	93	1.76	3.34
	hypertensive	23	46	61.2	141	2.45	3.45
50 ~ 59	normotensive	19	54	50.7	96	1.94	8.18
	hypertensive	61	55	52.3	141	2.86	3.16
60 ~	normotensive	19	66	51.7	97	1.93	3.04
	hypertensive	58	66	49.2	137	2.96	2.98

2. The relationship between blood pressure and cerebral circulation.[3)]

In order to know the correlation between blood pressure and cerebral circulation, taking the age factor into a consideration, we studied the relation of blood pressure and CBF in 3 groups, namely younger group of under 29 years of age, a middle age group from 30 to 49 and an advanced

MABP	CBF (average)	Number of cases
70	72.5	1
80	63.2	15
90	66.4	9
100	61.5	15
110	74.4	6
120	82.5	1
130		0
140	87.5	1
150	82.5	1

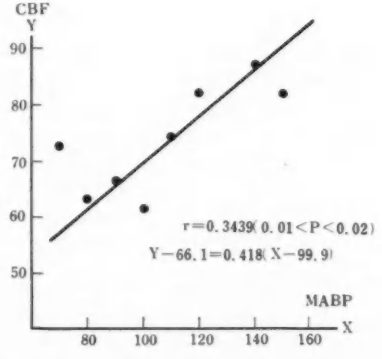


Fig. 2. Relationship between blood pressure and CBF (young group).

MABP	CBF (average)	Number of cases
60	57.5	3
70	42.5	3
80	56.3	17
90	54.4	16
100	57.7	21
110	60.8	3
120	60.0	2
130	65.6	4
140	59.0	4
150	61.3	4
160	60.8	3
170	57.5	1

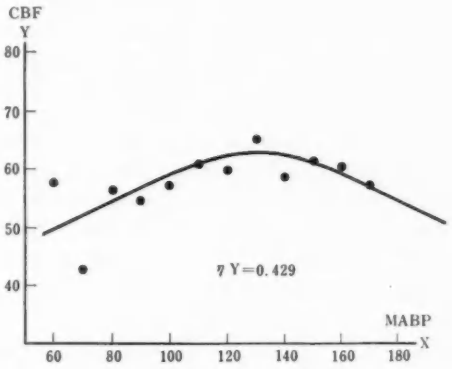


Fig. 3. Relationship between blood pressure and CBF (middle age group).

aged group above 50.

Generally, in the younger group, CBF increases in proportion to the blood pressure rises, so the rise of blood pressure is considered as one of the factors contributing to the increase in CBF (Fig 2). In the middle age group, the relation between blood pressure and CBF shows a curved line (Fig. 3), that is, in this group the rise of blood pressure not always results in an increase in CBF; on the contrary, sometimes the rise of blood pressure above a certain level (170 mm.Hg in systolic) may become a factor contributing to the decrease in CBF. It is supposed that this is a secondary phenomenon attributed to the spasms or sclerosis of arterioles in this age group. In the

MABP	CBF (average)	Number of cases
70	67.5	1
80	50.0	2
90	52.3	22
100	47.9	14
110	50.0	8
120	51.0	17
130	51.9	18
140	50.6	13
150	58.5	5
160	50.0	4
170	42.5	2
180	52.3	1

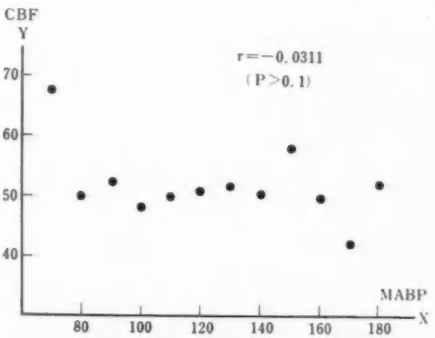


Fig. 4. Relationship between blood pressure and CBF (advanced age group).

advanced age group, the definite correlation between blood pressure and CBF is not found. As their cerebral sclerosis is advanced and the reaction of cerebral vessels to blood pressure is slowed down (Fig. 4), it is supposed that CBF is not greatly influenced by blood pressure. The problem of the relation between blood pressure and CBF with aging must be studied further.

3. The relationship between fat metabolism and cerebral circulation.[4]

The abnormality of fat metabolism is regarded as a pertinent cause for the development of atherosclerosis and as such it may be related to cerebral sclerosis. The values of serum cholesterol in patients with hypertension, cerebral sclerosis and cerebral apoplexy were compared with those in control group of the same age (Table IV). No difference of serum

Table IV. Cerebral Sclerosis and Total Serum Cholesterol (mg./100 ml.) (♂)

Age	40 ~ 59	50 ~ 59	60 ~ 69
Normal (control)	171±26 N=45	169±68 N=24	165 ± 23 N=10
Essential hypertension	169±87 N=45	171±23 N=45	179 ± 25 N=31
Cerebral sclerosis or hemiplegia	185±29 N=7	172±55 N=19	188±121 N=10

cholesterol level was found between the hypertensive group and the control group at each age. In the case of cerebral sclerosis and cerebral apoplexy, difference was not seen at the 50 year-old level, but at 60 year-old level only a slight increase in cholesterol level was found in cerebral sclerosis and apoplexy group in contrast to that of the control group of the same age.

Viewing the fat metabolism from the standpoint of cerebral circulation,

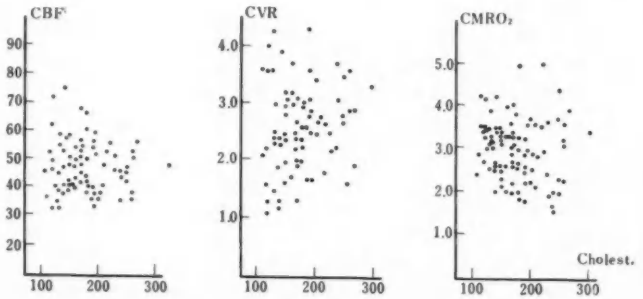


Fig. 5. Relationship between serum cholesterol and CBF, CVR and $CMRO_2$

cases with increased serum cholesterol showed a tendency of decrease in CBF and $CMRO_2$, and increase in CVR (Fig. 5). C/P ratio and lipoid index have no definite correlations with cerebral circulation.

In the younger and middle age groups, the serum cholesterol value increases with age, being accompanied by a concurrent increase in obesity. However, in the group above 70 years of age, which mostly consists of slender individuals, the cholesterol level is low. Therefore, among the subjects under 70 years of age, it might happen that serum cholesterol level has a negative correlation with CBF through the "age" and / or "obesity" factors. But, above 70 years old, this is not the case. In other words, the serum total cholesterol is not elevated in hypertension, cerebral arteriosclerosis and apoplexy as compared with control subjects of the same age. The author failed to find out a direct interrelationship between the cerebral arteriosclerosis and abnormalities in serum lipid level.

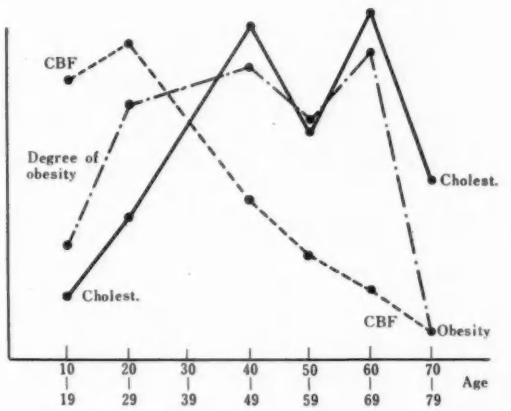


Fig. 6. Relations between serum cholesterol and CBF and degree of obesity.

4. The relationship between retinal finding and cerebral circulation.[5]

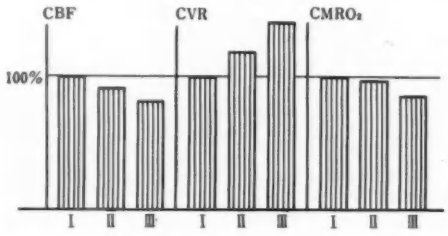
Provided that we can conjecture the diseases involving cerebral circulation from retinal findings, there is a decrease in CBF and $CMRO_2$ and a rise in CVR (Table V) in advanced degree of Keith-Wagener classification. But these relationships are no more than gross parallel connection. Similar relations are shown with Scheie's classification of retinal findings.

5. The relationship between clinical symptoms and cerebral circulation.[6]

From the standpoint of view that the clinical symptoms of cerebral sclerosis are caused by the disturbance of cerebral hemodynamics, subjective symptoms with hypertension were studied in relation to the cerebral circulation. In the middle age group, 40 to 59, in general, significant

Table V. Relationship between Retinal Finding and Cerebral Circulation

	I	II	III
	13	56	12
Number of cases	51	58	55
Average age	55.9	51.7	45.7
CBF	136	136	145
MABP	2.36	2.81	3.37
CVR	3.33	3.26	2.89
$CMRO_2$	Keith-Wagener		



decrease in CBF was recognized.

This is especially true when the subjective complaints of dizziness, numbness of extremities and failure of memory are present. In every case of the advanced age group, above 60, decrease in CBF and $CMRO_2$, and increase in CVR were observed, particularly when the disturbance of cerebral metabolism was remarkable. They often complain of a marked dizziness and failure of memory. In each age group, as a whole, patients with the above mentioned 3 symptoms usually show a severe disturbance in cerebral hemodynamics. From the results in our studies, subjective symptoms which related closely to cerebral sclerosis in hypertension were dizziness, failure of memory etc. The fact that these symptoms correlate with the disturbance of cerebral circulation and its metabolism appears to give an important knowledge for the treatment of cerebral sclerosis.

6. Cerebral hemodynamics of cerebral sclerosis.[5]

Hitherto we described the basic phenomena in connection with cerebral sclerosis from the consideration of cerebral circulation. Cerebral hemodynamics and metabolism in cerebral sclerosis were shown as a decrease in CBF and $CMRO_2$. The difference of these values was not shown to be remarkable between the aged normotensive and the aged hypertensive groups, but the degree of the decrease was greater in the order of hyper-

tension, cerebral sclerosis and cerebral sclerosis with hypertension. CVR increased in the hypertensive group and in the cerebral sclerosis group even when the cases without hypertension showed the high value (Table VI). Therefore, from the view point of cerebral circulation one may

Table VI. Cerebral Hemodymanics of Cerebral Sclerosis

	Normal old age		Cerebral sclerosis	
	normotensive	hypertensive	normotensive	hypertensive
No. of cases	10	21	9	13
Age	57	58	58	64
CBF	51.6	53.3	44.6	39.0
MABP	97	144	99	121
CVR	1.89	2.73	2.40	3.21
$CMRO_2$	3.08	3.09	2.74	2.46

diagnose the case as cerebral sclerosis in which a marked decrease in CBF $CMRO_2$ and a rise in CVR are present.

Treatment for Cerebral Sclerosis

Cerebral sclerosis is understood as an example of the syndrome caused

Table VII. Treatment of Cerebral Sclerosis

A. General treatment
   1. Moderation
   2. Diet
   3. Treatment of related illness (high blood pressure, obesity)

B. Anti-arteriosclerotic drugs

C. Treatment intending to increase the cerebral blood flow
   1. Papaverine hydrochloride
   2. ATP
   3. Acetylcholine
   4. Amyl nitrite
   5. Others

D. Metabolic accelerators of brain
   1. Thioctic acid
   2. ATP
   3. Co-carboxylase
   4. Pangamic acid
   5. Nicotinic acid
   6. Pantothenic acid
   7. FAD
   8. Orotic acid

E. Central nervous system stimulants

by several factors affecting sclerosis of cerebral vessels. So the fundamental principle of the treatment is primarily to treat the generalized arteriosclerosis itself and secondarily to treat the symptoms. Cerebral sclerosis is considered as an irreversible change and it seems to be impossible to recover from it sufficiently. In the Table VII, our course of the treatment for cerebral sclerosis is shown but we shall explain only about the items under C.

i) Cerebral Vasodilator[7]

The effects of papaverine hydrochloride, nicotinic acid, acetylcholine, amyl nitrite, Imidarine, ATP,[8] Kallikrein, Persantin and inhalation of carbon dioxide etc. on cerebral vessels were studied. Among them papaverine and inhalation of CO_2 caused a significant increase in CBF; acetylcholine, amyl nitrite and ATP given intravenously with glucose solution also produced an increase in CBF (Table VIII). Inspite of the

Table VIII. Effect of Vasodilator Drugs

	Method	Cases	CBF	MABP	CVR	$CMRO_2$
Papaverine	0.2 Gm. int. v. inj.	7	⇧	~	⇩	⇧
Nicotinic acid	20 mg. 〃	10	~	~	~	~
〃	100 mg. 〃	10	↓	↓	~	↑
Acetylcholine	0.1 Gm. subc. inj.	3	↑	~	↓	↑
Amylnitrate	1~2 Amp. inh.	2	↑	↓	↓	↑
2-Benzylimidazoline hydrochloride	10~20 mg. int. v. inj.	6	~	~	~	~
〃	10 mg. int. carot. inj.	9	~	~	~	↓
ATP	10 mg. int. v. inj.	10	~	~	↓	~
〃	20 mg. 〃	5	~	↓	↓	↓
ATP+40% Glucose 40 ml.	20 mg. 〃	10	↑	~	↓	⇧
Kallikrein	20 unit 〃	4	~	~	~	~
Vasculat	50 mg. subc. inj.	4	↑	↓	↓	↑
Persantin	10 mg. int. v. inj.	6	~	~	↓	↑
5~7% CO_2 moral subject	inhal.	5	⇧	⇩	↓	↑
hypertensive patients	〃	18	⇧	↑	⇩	↑
hemiplegic patients	〃	10	⇧	↑	↓	↑
40% Glucose	40 cc int. v. inj.	7	↓	↓	~	↓

⇧ ⇩ statistically significant

effects of nicotinic acid and Imidarine shown in the flushing of face, no change in CBF was recognizable. Accordingly, this finding indicates that intracerebral vessels do not respond in the same manner with vessels of the face. But when nicotinic acid was given to the patients with the symptoms of cerebral sclerosis in the daily dose of 20 mg. intracutaneously

or 50 mg. orally, improvements were obtained in cases with headache, heaviness of head and dizziness etc.

It has been known that the inhalation of CO_2 in high concentration (3–5%) has the strongest vasodilating action on cerebral vessels. By the inhalation of 5% CO_2 in healthy youth, a marked increase in CBF was found and an elevation of MABP and a decrease in CVR were also observed, and from these the dilatation of cerebral vessels was presumed. No remarkable change in $CMRO_2$ was found. Similar results were confirmed in the cases with hypertension and hemiplegic patients, but the degree of rise in blood pressure declined in the order as follows; normal youth, hypertension and hemiplegia.[9] It seems that the reaction of cerebral vessels in diseased individual is diminished in consequence of the progress of vascular sclerosis. And thus, this finding must be taken into consideration in connection with the treatment.

Among Xanthin-derivatives, vasodilator, caffein, aminophylline and oxyphylline produced a decrease in CBF and $CMRO_2$ and a rise in CVR.[7] So the use of these medicines in cases with cerebral sclerosis needs a precaution (Table IX).

Table IX. Effect of Xanthines

	Method	Cases	CBF	MABP	CVR	$CMRO_2$
Caffein	0.46 Gm. int. v. inj.	8	⇩	~	⇧	↓
Theophylline ethylendiamine	0.25~0.50 Gm. 〃	19	⇩	⇩	⇧	↓
Oxyethyl-theophylline	0.22 Gm. 〃	5	⇩	~	↑	↓
Diethyl-amino-ethyl-theophylline	0.5 Gm. 〃	6	↑	~	~	↑
7-(β-hydroxypropyl)-theophylline	0.2 Gm. 〃	10	~	~	~	~
Parmanil	2~4 ml. 〃	15	~	~	~	↓

ii) Accelerators of Cerebral Metabolism[10]

As accelerators of cerebral metabolism, various substances, i.e. vitamin B_1, co-carboxylase, FAD, thioctic acid, pangamic acid, nicotinic acid, nicotinamide, pantothenic acid and orotic acid were studied for their effects on cerebral circulation, and a significant increase in $CMRO_2$ was confirmed in the cases treated with co-carboxylase, thioctic acid and pangamic acid. FAD, nicotinic acid, pantothenic acid and orotic acid also produced an increase in $CMRO_2$ in a large number of cases (Table X). In addition to the drugs mentioned above, ATP, used as vascular dilator of brain, was demonstrated to accelarate the respiratory metabolism of the brain tissue by Warburg's method. As this result may be different according to the concentration of glucose as the basic solution, ATP (20 mg. with 40 ml. of 40% glucose) was injected to the

Table X. Effect of Vitamin B Group

	Doses	Cases	CBF	MABP	CVR	$CMRO_2$
Vitamin B_1	10 mg.	5	↓	↓	~	~
	100 mg.	4	~	↓	↓	~
Co-carboxylase	10 mg.	9	~	~	~	⇧
FAD	2 mg.	8	~	↓	~	↑
Thioctic acid	20 mg.	10	~	~	↓	⇧
Pangamic acid	20 mg.	13	~	~	↓	⇧
Nicotinic acid	20 mg.	10	~	~	~	~
	100 mg.	10	↓	↓	~	↑
Nicotinamide	100 mg.	5	~	~	↓	~
Pantothenic acid	20 mg.	6	↑	~	↓	↑
Orotic acid	100 mg.	7	~	~	↓	↑

patients which resulted in an increase in CBF, a decrease in CVR and a significant increase in $CMRO_2$.

Therefore, the effectiveness of ATP is thought to be due to a change following the rise in cerebral metabolism rather than primary vasodilation. By giving thioctic acid (25 mg.) intravenously with glucose in normal saline solution for cerebrovascular accidents, effectiveness on the disturbance of sensorium or speech and a failure of spontaneity were found.

A new mixed preparation, which is made from papaverine that has demonstrated to have a vasodilating effect on the cerebral vessel, thioctic acid having an accelerating action on cerebral metabolism and nicotinic acid that has a peripheral vasodilating action and is regarded as effective on symptoms of cerebral sclerosis, was given and the clinical effects was observed. More than 70% of the symptoms, i.e. headache, heaviness in head, feeling of the rushing of blood, stiffness in the shoulders, cold feeling in the extremities, weariness and depressive feeling, etc. were improved. But after administration of this drug for a week, a marked change in cerebral circulation was not found. As a result, when relatively small quantity of them (papaverine, thioctic acid and nicotinic acid) is given orally, a clear cut change will not be recognized in the value of cerebral hemodynamics. But as this preparation was effective to clinical symptoms, it may safely be said that the use of such preparation for cerebral sclerosis is reasonable.

iii) Central Nervous System Stimulants[11]

Since cerebral sclerosis is often accompanied by depressive feeling, the application of new central nervous system stimulants including Pipradrol, Methylphenidate, Cafilon, Dimethylaminoethanol, Metrazol, Megimide, γ-Aminobutylic acid and sodium glutamate was made and their effectiveness was observed. Piprodrol, Dimethylaminoethanol and γ-Aminobutylic acid did not produce any change in cerebral hemodynamics. CBF was increased

and $CMRO_2$ was unchanged by methylphenidate. In cases in which Cafilon and Metrazol were used, they produced an increase in $CMRO_2$ and no change in CBF, though these variations were not quite significant. With megimide, an increase in CBF and $CMRO_2$, and with sodium glutamate a decrease in CBF and $CMRO_2$ were observed (Table XI)

Table XI. Effects of Central Nervous System Stimulants on Cerebral Circulation

		CBF		MABP		CVR		$CMRO_2$		CRQ	
		B	A	B	A	B	A	B	A	B	A
Pipradrol	int. 4 mg. → 7 days	45.4	46.8	122	125	2.82	2.70	30.8	3.21	1.05	0.93
Methyl-phenidate	int. 40 mg. → 7 days	51.8	60.2	117	119	2.29	2.04	3.04	2.90	1.03	1.06
Cafilon	int. 4 mg. → 7~14 days	52.9	53.2	120	100	2.25	1.96	2.78	3.70	0.97	0·96
Dimethyl-aminoethanol	int. 40 mg. → 7 days	45.8	42.8	120	120	2.70	2.84	2.68	2.70	1.06	1.00
Megimide	Labona inj. → 10 mg. inj.	33.7	43.0	118	113	3.84	3.13	2.02	2.84	0.90	1.04
Metrazol + Nicotinic acid	int. 300 mg. / 150 mg. → 7~14 days	51.2	53.3	125	118	2.57	2.26	3.33	4.17	0.94	1.05
Na-glutamate	10 mg. + Ringer sol. inj.	50.4	44.1	95	104	1.92	2.37	3.11	2.67	0.95	0.86
GABA	int. 12 tab. 7~14 days	59.0	58.4	124	127	2.32	2.35	4.06	4.42	1.96	1.06

Note: B: before medication A: after medication
int.: interrally inj. intravenous injection

However, as the number of experimental cases was small, further investigation is indicated before any conclusion is made. From the results of our studies it may be concluded that these new central nervous system stimulants do not have remarkable effect on cerebral circulation and metabolism (by N_2O method) despite their effect on the feeling of well being. Recently, a simultaneous application of the control nervous system stimulants and cerebral vasodilator to the cerebral sclerotic psychical symptoms is recommended as effective. When a tablet which contains 100 mg. of metrazol and 50 mg. of nicotinic acid was given 3 times per day for 3 to 7 days to the patients with emotional disturbance, depressive feeling, and with inconstant psychic symptoms, i.e. headache, heaviness of head and sleeplessness and others, some effectiveness was observed but it was ineffecive in cases with failure of memory and dementia. Between the improvement of symptoms and the increase in cerebral metabolism by

N_2O method, there was no parallel relation but an average elevation of $CMRO_2$ at the rate of 25% was found.

Conclusion

(1) Hemodynamics of the brain in different diseases were studied by N_2O method together with the classification of the term "cerebral sclerosis". The diagnosis of cerebral sclerosis may be made when a marked decrease in CBF and $CMRO_2$ and a rise in CVR are observed in an individual above 40 years of age.

(2) The treatment for the different types of cerebral lesions was described mainly based on the results of our own study. The value of the treatment using cerebral vascular dilators and cerebral metabolic accelerators was discussed.

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Pathogenesis of the Acute Pulmonary Edema Occurring after Brain Operation and Brain Trauma

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By investigating the autopsy cases as well as clinical cases, it was found that the occurrence of the pulmonary edema following the brain damage was higher when it was compared with that of other diseases. In addition, clinical cases of the pulmonary edema occurring after various operations have been studied in detail and classified into 3 groups: (1) that occurring after brain operation and brain trauma, (2) that occurring after cardiopulmonary operation of cases with pulmonary circulatory disturbances, (3) that occurring after abdominal operation of cases with metabolic disorders. In order to clarify the mechanisms of occurrence of the pulmonary edema, studies were undertaken on the pulmonary vascular innervation and a pulmonary edema of the central nervous system in origin was experimentally produced. Examining the pathophysiology of the pulmonary edema in detail, some knowledges have been obtained about pathogenesis of an acute postoperative pulmonary edema.

STUDY of an acute pulmonary edema occurring after brain operations and brain traumas is one of the very difficult problems.[1)-7)] Despite the extensive studies in the past, the mechanism of its occurrence has not been well elicited.[6),8)-18)] One of the reasons for the failure in clarifying the mechanism is that the occurrence of pulmonary edema is too rapid and too severe to make clinical investigation in detail. Another reason is that it is extremely difficult to produce pulmonary edema experimentally as exactly the same as in postoperative cases.[19)-25)] After many attempts we have finally overcome these difficulties and succeeded in clarifying the pathogenesis of the postoperative pulmonary edema, especially that occurring after brain operation as well as brain trauma both clinically and experimentally.

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Materials and Methods

1) Analysis of autopsy cases as well as clinical cases of the acute pulmonary edema

The statistical analysis was carried out in a total of 1,355 autopsy cases at the Pathological Department, University of Kanazawa.

46 clinical cases of the pulmonary edema were studied morphologically (Table II). They consist of 35 cases of the acute postoperative pulmonary edema from 1,389 operations and 11 cases of the acute pulmonary edema as a complication of the cerebral trauma which were dealt with at the Department of Medical Jurisprudence, University of Kanazawa (Table III).

2) Methods for studying the innervation of the pulmonary vessels

Twenty-five adult dogs were used for the experiments. Under the anesthesia of intramuscular injection of Ravonal 30 mg./Kg., the animal was stabilized in a stereotaxical apparatus. The right heart catheterization was done for recording the pulmonary arterial pressure. The craniotomy was made. A stimulating electrode was inserted into several portions of the brain of the dog. The electrode was a coaxial needle with enamel coating, made of stainless steel, 1 mm. in diameter. As the stimulation, the square wave pulses of 15 volts, 100–120 c.p.s., and 1 msec. were used for 15, 30 or 60 seconds. The alteration of the pulmonary arterial pressure subsequent to the stimulation was recorded through the catheter in the pulmonary artery. The systemic arterial pressure and respiration were simultaneously recorded. The efferent pathway in the innervation of the pulmonary vessels was traced by observing the responses of the pulmonary arterial pressure to the stimulation, when the vagus nerve, the spinal cord and the brain stem were severed at the several levels. The afferent pathway in the innervation of the pulmonary vessels was traced in the following way: a pair of hooks of silver wire was placed on the pulmonary branches of the vagus nerve for the stimulation, which was the square wave of 0.2 msec. in duration delivered from the isolation unit. A silver electrode of tip diameter 5–10 μ with glass coating was inserted in several portions of the medulla, and the evoked potential was picked up subsequent to the stimulation. The electrodes, used both for the stimulation and for the pick-up of the evoked potential were put on a direct electric current, and necrotic foci were made electrolytically at the tip of the electrodes. Thus the sites of the stimulation and the pick-up were determined anatomically after sacrificing the animals.

3) Experimental production of the pulmonary edema of cerebral origin

Under the frontal craniotomy, the electrode 5 mm. in diameter was inserted into the preoptic area and bilateral preoptic areas were completely destroyed by electrocoagulation with an electric current of 7 mA. for 15–20 seconds.[26)–28)] The characteristic type of the pulmonary edema was successfully produced by this procedure.

4) Methods for studying pathophysiology of the experimental pulmonary edema

The following methods were used for the measurement pertinent to the study

of pathophysiology. Pulmonary circulation; right heart catheterization. Pulmonary circulation time and pulmonary blood volume; Stewart's method using P^{32} labelled red cells. Plasma colloidal osmotic pressure; Biuret's method and Wells & Youman's formula. Circulating blood volume; P^{32} labelled red cells. Extracellular fluid volume; Crandal & Anderson's method. Tissue water volume; Eaton's method. Electrolytes in plasma, urine and tissue; Na, K: flame photometer, Cl: Schales & Schales's method. Water exchange in the lung; pulmonary dilution curve by P^{32} and Na^{24} and Aviado's method. Pulmonary lymphatic flow amount; direct measurement by means of canulation into the right lymph duct. Behaviors of reticular fiber of the alveolar wall; silver impregnation. Permeability of the pulmonary capillary; injection of trypan blue into the pulmonary artery. VDM (Ferritin) in blood and liver tissue; electrophotometry using α, α'-dipyridyl. Activity of fibrinolytic ferment; MacFarlane's method. Histamine amount in the lung; Satake's bioassay method. Free catecholamine in urine; Euler-Floding's method. Antidiuretic hormone in blood; Lloyed & Lobotsky's method. 17-OHCS in blood; Sweet & Takeda's method. 17-KS in urine; Holtroff & Koch's method. Renal circulation; sodium paraminohippurate and sodium thiosulfate clearance method by Smith's continued dropping injection. Hepatic circulation; Bradley's method. Activity of phosphatase in the lung and liver tissue; staining by a modified method of Gomori. Activity of 5-nucleotidase; McManus's staining. RNA: staining by Kurnick's pyronin-methylgreen method and Feulgen's method. Activity of lipase; a modified method of Gomori using Tween 20, 40, 60 and 80. Polysaccharides in tissue; McManus's PAS staining. Glycogen in tissue; Bensley's method. Lipid in tissue; Daddi's sudan III staining, Herxheimer's sudan IV staining and Lisbon's sudan black B staining. Fatty acid; histochemical method by Okamoto, Ueda & Kato and round paper chromatography by Kurono.

Results

I. Observations of Autopsy Cases (Table I)

A total of 1,355 autopsy cases died of various diseases were reviewed and investigated the incidence of combination of the pulmonary edema. Eight per cent of those who died of abdominal diseases were accompanied by the pulmonary edema, while 28% of those who died of organic lesions of the brain had the pulmonary edema. Most of the lesions of the brain accompanying the pulmonary edema were located near or around the internal capsule, the lentiform nucleus and the third ventricle of the brain. Accordingly, it may be assumed that some lesions in these areas of the brain might have something to do with the development of the pulmonary edema.

II. Classification of Clinical Cases of Postoperative Pulmonary Edema (Table II)

Though an acute pulmonary edema appeared in a very wide variety of conditions, it was classified into 3 groups according to the similarity of the histological findings in our 46 cases: (1) that occurring after a brain

Table I. Incidence of Pulmonary Edema in Autopsy Cases

				Cases	accompanied by pulmonary edema		
Autopsy cases 1,355	Diseases of central nervous system 172	Lesions of brain substance 92	Near or around 3rd ventricle, internal capsule, N. lentiformis	27	18	(67%)	48 (28%)
			Other Parts	26	7	(27%)	
			Diffuse lesion	36	8	(21%)	
		Lesion of meningea		76	14	(18%)	
		Lesion of spinal cord		4	1	(25%)	
	Cardiovascular diseases			82	19	(23%)	
	Renal diseases			44	7	(16%)	
	Other diseases 1,057	Respiratory apparatus		556	17	(3%)	85 (8%)
		Digestive system, liver and spleen		235	41	(17%)	
		Generalized malignant tumors		33	3	(9%)	
		Hematopoietic organs		25	6	(24%)	
		Intoxications		17	7	(41%)	
		Other diseases		191	11	(6%)	

operation as well as brain trauma, (2) that occurring after an operation of cases with cardiopulmonary diseases accompanied by pulmonary circulatory disturbances, and (3) that occurring after an abdominal operation of various diseases accompanied by metabolic disorder such as hypoalbuminemia, anemia and hepatic or renal disturbance.

Table II. Classification of Clinical Cases of Postoperative Pulmonary Edema

1st Group:	Those accompanied by nervous disturbance	19 Cases
2nd Group:	Those accompanied by pulmonary circulatory disturbance	19 Cases
3rd Group:	Those accompanied by metabolic disorder	8 Cases
	Total	46 Cases

As to the features of the pulmonary edema occurring after an operation for diseases of the central nervous system, there appeared a marked congestion of the pulmonary vascular system and floating of red cells was found in the alveoli. The exudation of a liquid component in the alveoli was clearly seen (Fig. 1). In the cases of pulmonary edema after an operation for cardiopulmonary diseases, a congestion of the pulmonary vascular system and hemorrhage into the the alveoli were remarkable. This was particularly true in the cases where there was pulmonary hypertension before the operation. In such cases the fibrosis of the blood vessels was seen in addition to the above mentioned hemorrhage and the congestion.

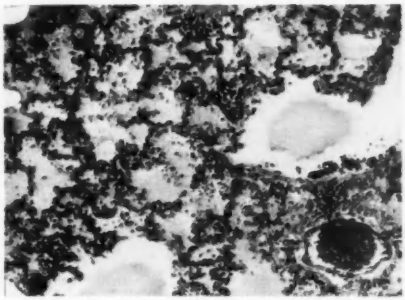


Fig. 1. Congestion, floating of red cells and exudation of liquid component in the alveoli in a case of pulmonary edema after the brain operation (bilateral frontal lobotomies), Case 7, F. M. 4 y. ♀, H-E, ×90.

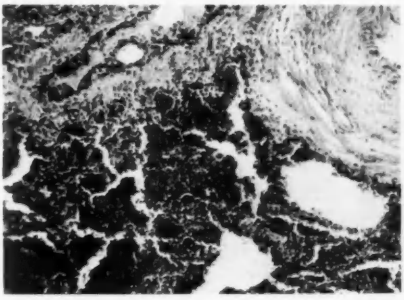


Fig. 2. Remarkable hemorrhage into the alveoli with fibrous thickening of the vessel wall in a case of pulmonary edema after the cardiac operation (congenital cardio-vascular malformation; truncus arteriosus), Case 22, N. K. 6 y. ♂, H-E, ×90.

Though the exudation of liquid component into the alveoli was also seen, its degree was much less than that in cases of brain lesions (Fig. 2). In the cases of pulmonary edema after an operation of abdominal diseases accompanying hypoalbuminemia, anemia and hepatic or renal disturbance, the congestion was not remarkable, but a high degree of exudation of liquid component into the alveoli was observed (Fig. 3).

Fig. 3. High degree of exudation of liquid component into the alveoli without congestion in a case of pulmonary edema after abdominal operation (gastric cancer with metabolic disorder), Case 39, S. O. 55 y. ♀, H-E, ×90.

In order to determine the incidence of these 3 types, a calculation was made about the ratios of the numbers of major brain, cardiopulmonary and abdominal operations to the numbers of occurrence of pulmonary edema. These were 12%, 3% and 1%, respectively (Table III). It is worthy of note that the incidence of the postoperative pulmonary edem in brain

surgery is significantly higher than those in other types of operations.

Table III. Incidence of Postoperative Pulmonary Edema in Clinical Cases

		Accompanied by pulmonary edema
Brain operation and brain trauma	67 Cases	8 Cases (12%)
Thoracic surgery	619 Cases	19 Cases (3%)
Abdominal operation	703 Cases	8 Cases (1%)
Total	1,389 Cases	35 Cases

III. Innervation of the Pulmonary Vessels

For the purpose to clarify the relationship between the nervous system and the development of the pulmonary edema, an investigation about the innervation of the pulmonary vessels was performed.

From this investigation 2 terminals were found by silver impregnation: myelinated afferent one and nonmyelinated efferent one around capillaries of the pulmonary vessels (Fig. 4). The diameter of the nerve fibers of the

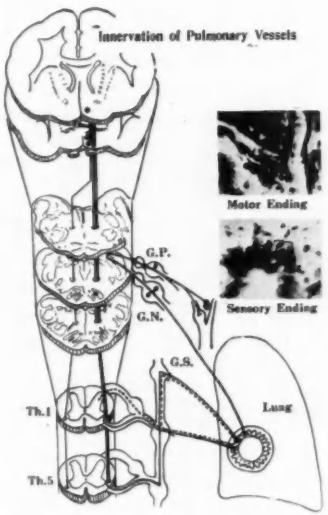


Fig. 4. Innervation of pulmonary vessels.

sensory ending varied from 4 to 8 μ. The ascending afferent pathway from this ending was traced by picking up the evoked potential in the medulla to the stimulation of the pulmonary vessels. The fibers were assumed to ascend mostly in the vagus nerve and attain to the infrasolitary nucleus and the ventral portion of the lateral nuclei of the solitary tract. The

diameter of the fibers was calculated as 6 to 8 μ from the conduction velocity. It was considered that there might be afferent pathways other than the one ascending along the vagus nerve, and they might run in the sympathetic or sinus nerve, since a slight elevation of the pulmonary arterial pressure was seen subsequent to an adequate stimulation of the pulmonary hilum even after bilateral cervical vagotomies and since the pulmonary arterial pressure was elevated during the stimulation after a complete section of the spinal cord at the level of C_1. It was clarified from the decerebration experiments that the afferent pathway ascending the vagal nerve passed through the nuclei around the solitary tract to the midbrain.

Seeking the portion in the cerebrum and the brain stem at which a stimulation caused the selective elevation of pulmonary arterial pressure, it was found that an electrical stimulation of the nucleus preopticus principalis and nucleus preopticus magnocellularis of the preoptic area induced a characteristic elevation of pulmonary arterial pressure (Fig. 5).

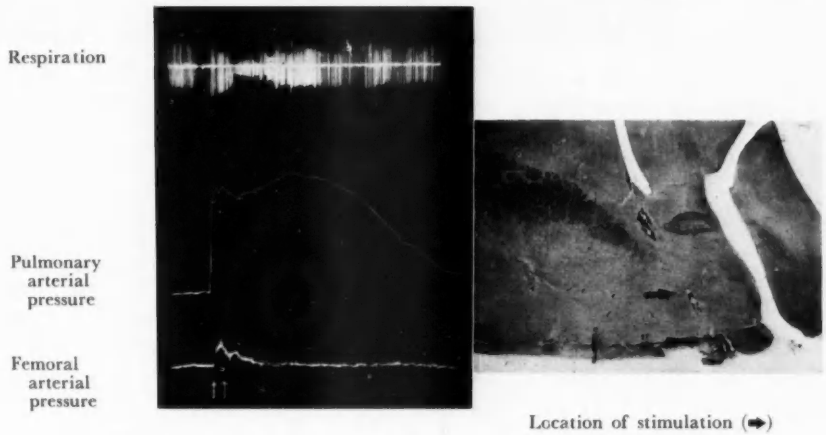


Fig. 5. Changes in pulmonary arterial pressure caused by stimulation of the preoptic area (N. preopticus principaris).

By the stimulation of other portions around these nuclei, namely the hypothalamus, the caudate nucleus and the internal capsule, there was no rise of pulmonary arterial pressure. The efferent pathway from these nuclei of preoptic areas passed the reticular formation ventral to the tegmentum at the level of the pons and passed through the ventral portion of the reticular formation at the level of the medulla, descending mostly ipsilaterally and partially contralaterally, passed through the bilateral anterolateral funiculi of the spinal cord and entering the sympathetic nerve from the spinal cord at the portion between C_1 and Th_5, distributed to the pulmonary vessels (Fig. 4 and 6).

It could be concluded that there were both higher and lower centers on the reflex arc which consists of afferent and efferent

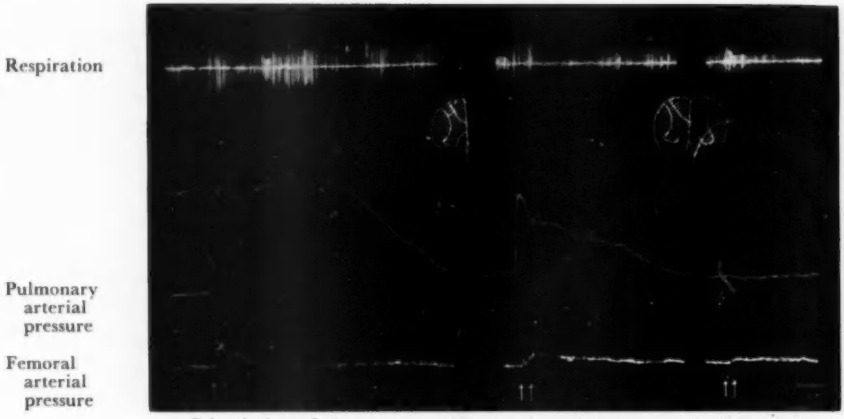

Respiration
Pulmonary arterial pressure
Femoral arterial pressure
Stimulation of the preoptic areas
Hemisection of the spinal cord of stimulated side
Ipsilateral hemisection and contralateral anterior chordotomy

Fig. 6. Changes in pulmonary arterial pressure subsequent to stimulation of the preoptic areas and section of the spinal cord.

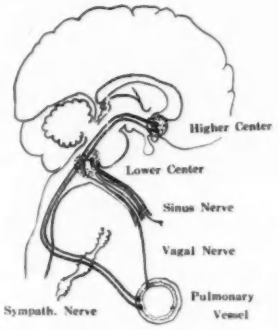


Fig. 7. Reflex centers of innervation of the pulmonary vessels clarified by section and stimulation experiments.

pathways of the pulmonary vascular innervation (Fig. 7). The higher center of the reflex arc where the afferent pathway ascends the vagal nerve was situated in the nuclei of the preoptic areas. The efferent pathway starting from this center passed through the pons, the medulla and the upper spinal cord and, entering the efferent sympathetic nerve, was distributed to the pulmonary vessels. On the other hand, the lower

Table IV. Site of Attacks in Cases of Pulmonary Edema after Brain Operation and Brain Trauma

	Case	Diseases	Operation
1st group; relating to preoptic area and hypothalamus.	3. T. O. 50	Hypophyseal tumor	Frontal craniotomy, exstirpation of tumor
	4. K. K. 18	Malignant craniopharyngeoma	Frontal craniotomy, resection of tumor
	5. T. F. 53	Basis fracture	
	6. T. D. 63	Hemorrhage of right lateral ventricle and 3rd ventricle basis	Bilateral frontal lobectomies
	7. F. M. 4	Traumatic aphasia	
	9. K. S. 48	Contusion of left frontal and temporal lobes	
	10. K. M. 42	Subarachnoidal and intraventricular bleeding	
	12. T. T. 19	Contusion of right frontal and temporal lobes	
	13. M. S. 28	Contusion of inferior part of left frontal lobe and olfactory region	
	14. J. Y. 43	Contusion of left frontal and temporal lobes	
	15. M. M. 37	Contusion of left frontal and temporal lobes	
	16. H. M. 32	Hemorrhage of inferior part of right frontal lobe and in ventricle	
	17. H. M. 69	Contusion of left frontal and temporal lobes	
	18. K. S. 35	Pressures of right frontal and temporal lobes by the hematoma	
	19. W. K. 35	Contusion of left hemisphere, especially frontal half	
2nd Group; relating to pons and medulla.	1. F. Y. 16	Tumor in lateral ventricle	Craniotomy
	2. K. H. 48	Cerebellar pontine angle tumor	Suboccipital craniotomy, resection of tumor
	8. M. O. 4	(Bulbar palsy symptom)	Lobotomy
	11. Y. M. 56	Hematoma of frontal portion, bleeding of cerebral peduncle and pons	

center of the reflex arc where the afferent pathway ascends the sympathetic nerve or sinus nerve was situated in the medulla and from this the efferent pathway turned immediately into the efferent sympathetic fibers.

We have also studied a participation of the nervous factor in the development of the pulmonary edema in our clinical cases (Table IV). Among 46 clinical cases, 19 cases have developed the edema after a brain operation or brain trauma. The sites of lesions in these cases have been thoroughly investigated. There have been 8 cases (12%) of the postoperative pulmonary edema among 67 cases of brain operation during past 5 years. Five cases of them were those developed the edema after the operations of malignant craniopharyngioma, hypophyseal adenoma with Cushing's syndrome and brain stem lesion and after frontal lobotomy. These foci were adjacent to the preoptic areas and the hypothalamus. The operations were performed through frontal craniotomy, approaching

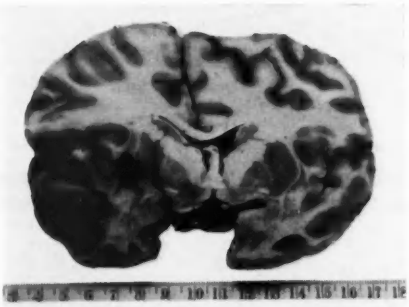


Fig. 8. Location of foci of a case of brain trauma accompanied by pulmonary edema. There is seen the contusion extending from the temporal lobe to the striate body (case No. 12. T. T. 19 y. ♂).

Fig. 9. Location of foci of a case of brain trauma accompanied by pulmonary edema. There is seen hemorrhagic focus in the pons (case No. 11, Y. M. 56 y. ♀).

to the optic chiasma by lifting orbital side of the frontal lobe. In the remaining 3 cases, the pulmonary edema occurred after the operations for cerebellar tumor, pontine tumor and lateral ventricular tumor having relations to the pons and the medulla. These operations were carried out mostly by suboccipital craniotomy. Among the 11 cases died of brain trauma accompanied by the pulmonary edema, 10 had the lesions in the vicinity of the preoptic areas, and one in the medulla (Fig. 8 and 9).

Summarizing these findings, it was found that the foci or the operative attacks in some cases had a close relation to the higher center in the

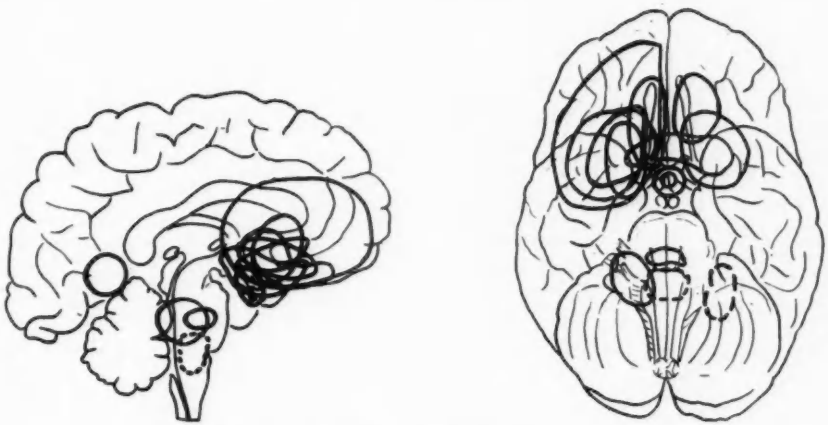


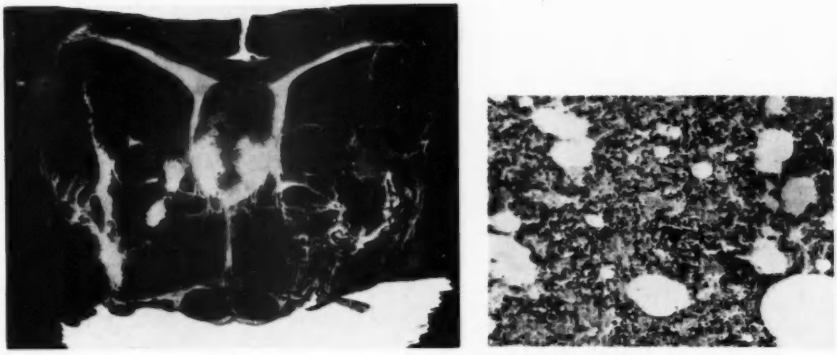
Fig. 10. Location of foci of cases of the central nervous diseases accompanied by pulmonary edema.

preoptic areas which had been experimentally disclosed, and the foci or the operative attacks in another group had close relation to the lower center in the medulla (Fig. 10).

IV. Pathological Physiology of Experimentally Produced Pulmonary Edema

The pulmonary edema could be produced, bringing about changes in the pulmonary circulation, by destroying any of the courses of the pulmonary vascular innervation.

When the bilateral preoptic areas, which are regarded as the higher center of the pulmonary vascular innervation, were completely destroyed by an electrocoagulation, the pulmonary edema occurred frequently (Fig. 11). In order to produce this type of the pulmonary edema, it was necessary to destroy the both sides of the preoptic areas completely. Destruction of one side of the preoptic areas did not cause the pulmonary edema. Furthermore, destruction of other portions of the brain such as the hypothalamus and the cerebral cortex did not produce any pulmonary edema.



(a) (b)

Fig. 11. Destroyed portion of the bilateral preoptic areas to produce pulmonary edema and histological figures of the lung of pulmonary edema caused by the lesions.

(a) Frontal section slightly magnified.

(b) Notice the exudation of fluid into the alveoli as well as the bronchioli and the hemorrhage in interstitium (×90).

When the bilateral preoptic areas were destroyed, the animal could hardly survive for a long time and died 6–7 hours after the operation. The edema occurring in such a case was mostly involved in the lung. Moreover, histology of thus experimentally produced pulmonary edema was exactly the same as that of the clinical pulmonary edema occurring after brain operation or brain trauma (Fig. 10 and 11).

In the cases of experimentally produced pulmonary edema by complete destruction of the bilateral preoptic areas, various pathophysiological responses have been observed in detail: Respiration was markedly suppressed. Oxygen consumption and arterial blood oxygen saturation became lower. A gradual fall in arterial pressure with decreased cardiac output was seen. Pulmonary arterial pressure was elevated and reached to 350–450 mm. H_2O (Fig. 12). This marked elevation of pulmonary arterial pressure was the characteristic phenomenon in the bilateral preoptic lesions. The destruction of other portions of the brain stem or the unilateral preoptic lesion did not raise pulmonary arterial pressure. Pulmonary vascular resistance increased considerably, pulmonary circulation time became prolonged, and pulmonary blood volume also seemed to be increased (Fig. 12). Hepatic blood flow as well as renal blood flow decreased remarkably, and urine excretion became extremely low (Fig. 13). Serum protein and colloidal osmotic pressure of plasma did not show any remarkable changes. The increase in the extracellular fluids was slight, but the fluids in the tissue stroma showed a remarkable increase due to a decreased circulating

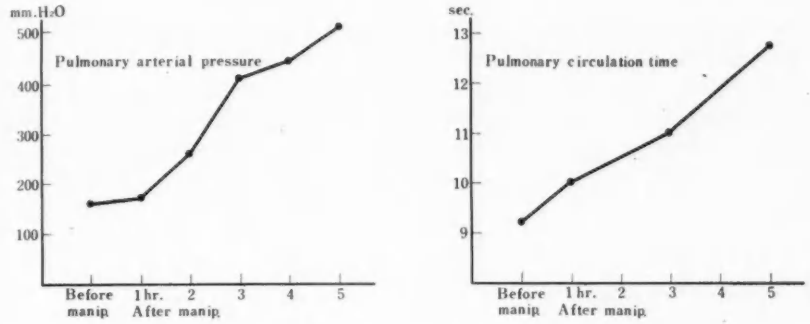


Fig. 12. Changes in pulmonary circulation in the process of pulmonary edema produced by bilateral preoptic lesions.

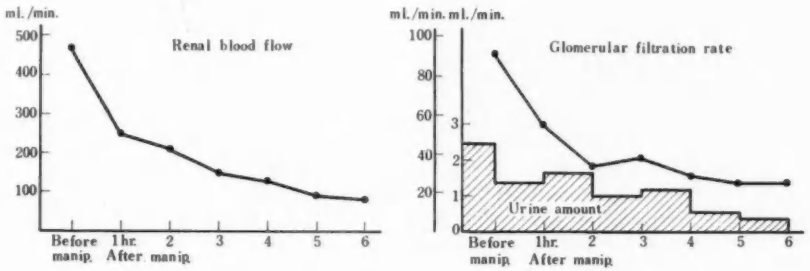


Fig. 13. Changes in renal circulation in the process of pulmonary edema produced by bilateral preoptic lesions.

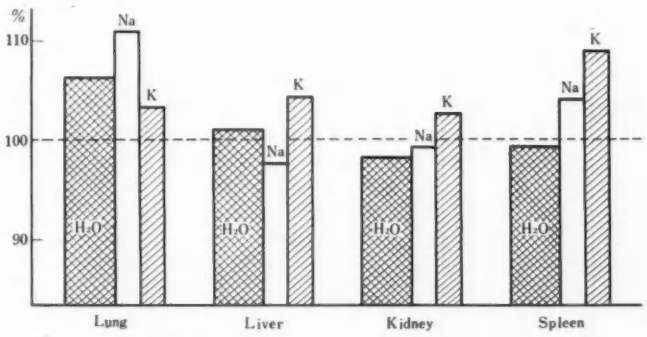


Fig. 14. Tissue water volume and electrolytes of various organs in the process of pulmonary edema produced by preoptic lesions, showing the increase and the decrease in pulmonary edema with percentage by making normal value 100%.

blood volume. As to the changes of electrolytes in plasma and tissues, the retention of sodium in plasma and the lung was remarkable. Tissue water was also increased in the lung (Fig. 14). The pulmonary dilution curve which was made by an incorporation of Na^{24} and P^{32} labelled red cells showed transcapillary water exchange and the dynamics of intrapulmonary water shift clearly (Fig. 15). Both the exudation of water into the lung

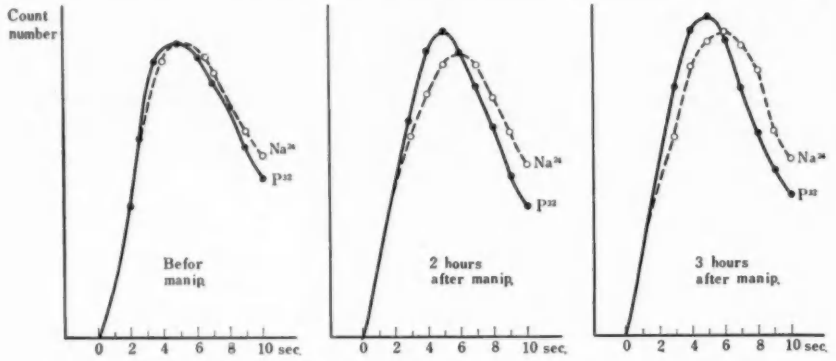


Fig. 15. Dilution curve of the lung by means of Na^{24} and P^{32} labelled erythrocytes in the progress of pulmonary edema produced by preoptic lesions. The both curves make approximately same course before operation. After preoptic lesions, Na^{24} curve shifts to the right showing the increase in water exchange. P^{32} counts over Na^{24} counts implies that transudation of water surpasses reabsorption in the pulmonary capillaries.

and the absorption from the lung were going on rapidly and vigorously in the early stage, while in the late stage the transudation of water overwhelmed the reabsorption of water resulting in a prominent pulmonary

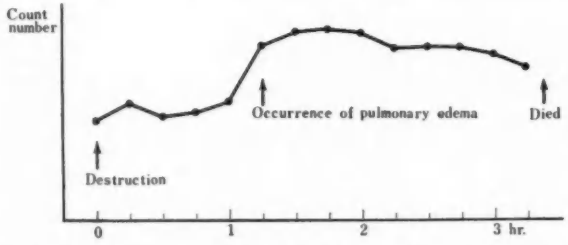


Fig. 16. Appearance of Na^{24} in the blood after injection of Na^{24} into the bronchi, in the progress of pulmonary edema produced by preoptic lesions. In the progress of pulmonary edema, the count number increases.

In the advanced stage of pulmonary edema the count number is refrained from increase, the curve becomes flat and the count number decreases gradually.

edema. When the distribution of water to various tissues was traced by Aviado's method, the muscle reserved much water in the case of simple transfusion, while in the case of bilateral preoptic lesions, water was accumulated into the lungs selectively, producing the pulmonary edema (Fig. 16). When Na^{24} was injected into the alveoli, the absorption curve of blood rose in the early stage of pulmonary edema, but at the maximal stage the absorption was suppressed producing a flat curve. The pulmonary lymphatic flow increased from time to time, but eventually it began to decrease. The reticulate fiber of the alveolar wall showed some swelling,

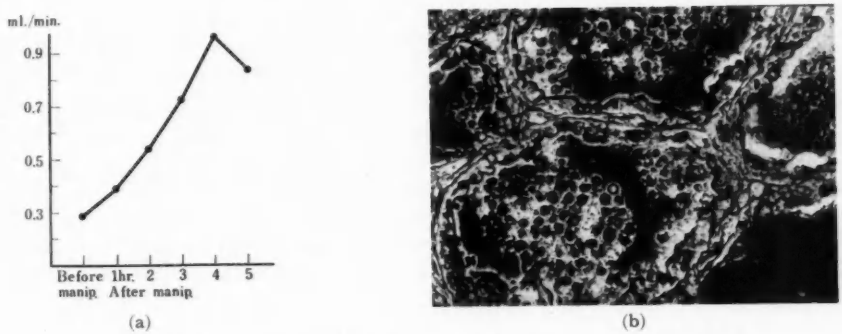


Fig. 17. Changes in pulmonary lymph flow and reticular fiber of the alveolar wall in the process of pulmonary edema produced by preoptic lesions.

(a) Pulmonary lymph flow.

(b) The reticular fiber of the alveolar wall shows swelling, broadening and breaking (×180).

broadening, and breaking which nicely represent the changes in the pulmonary lymphatic flow (Fig. 17). 17-Hydroxycorticosteroid in blood, 17-ketosteroid in urine and antidiuretic substance in blood increased from the beginning (Fig. 18). It is worthy of note that these hormonal changes

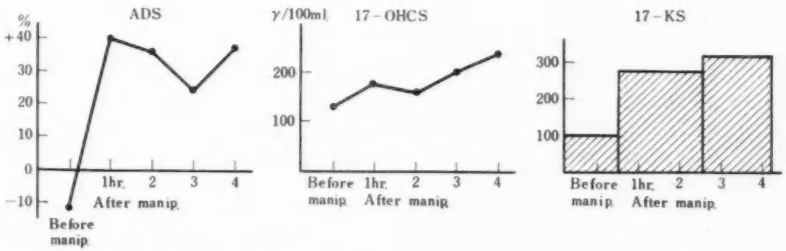


Fig. 18. Endocrine changes in the process of pulmonary edema produced by preoptic lesions (A. D. S.: Anti-diuretic substance).

occurred immediately after the production of the bilateral preoptic lesions. This might indicate that the damage of the preoptic areas would influence directly upon the hormonal regulation, inducing the hormonal unbalance. VDM decreased in the liver and increased in the blood. The activity of

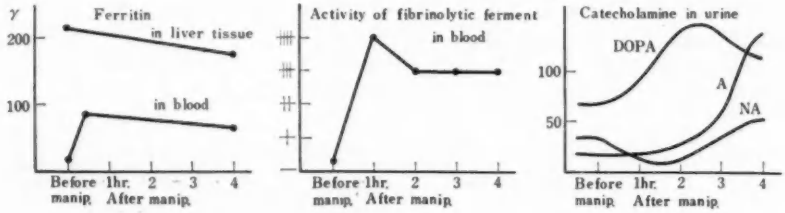


Fig. 19. Changes in ferritin, fibrinolytic ferment and catecholamine in the process of pulmonary edema produced by preoptic lesions.

fibrinolytic enzyme became strong, histamine of the lung tissue and free catecholamine in urine increased markedly from the beginning (Fig. 19). The permeability of the pulmonary capillaries became increased with the lapse of time as seen in passing of the trypan blue through the pulmonary artery. Phosphatase activity, 5-nucleotidase activity, RNA metabolism, lipid metabolism and polysaccharide metabolism in the tissues of the lung and the liver became vigorous in the early stage of development of pulmonary edema, but, as time went on they became unbalanced and weakened (Fig. 20).

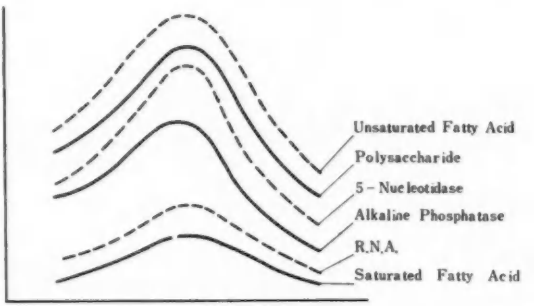


Fig. 20. Changes in histochemistry in the process of pulmonary edema produced by preoptic lesions.

When the pulmonary edema was induced by the stimulation on the sympathetic nerve which is a part of the reflex arc of the pulmonary vascular innervation, there were little changes in plasma colloidal osmotic pressure, urinary volume, water and electrolytes in both urine and tissues

and the permeability of the pulmonary vessels. However, there was an elevation of pulmonary arterial pressure during the stimulation.

When the vagus nerve was severed at the cervical region and its proximal end was stimulated, pulmonary edema appeared. In this case, pulmonary arterial pressure became elevated during the stimulation and plasma colloidal osmotic pressure was lowered. Water and sodium in the lung tissue were increased slightly. There was little change in the permeability of the pulmonary vessels.

For the purpose of comparing the pathophysiological characteristic of the pulmonary edema of cerebral origin with that of the other type, we have produced the experimental pulmonary edema corresponding to the second group of clinical postoperative pulmonary edema; that occurring after an operation of the cases with cardiopulmonary diseases accompanying some pulmonary circulatory disturbances. This type of the pulmonary edema was reproduced by the pneumonectomy in combination with low oxygen respiration, inspiratory resistance, and massive intravenous infusion of the saline solution.[19] Pathophysiology has been found to be as follows: there were observed a decreased oxygen saturation of the peripheral arterial blood, lowered peripheral arterial pressure and a gradual fall of cardiac output. Following a massive intravenous infusion of the saline, a transient increase in the circulating blood volume occurred, but disappeared gradually as the fluids in the tissue stroma became increased. The pulmonary lymphatic flow increased. Pulmonary arterial pressure rose immediately after an operation and remained high. Colloidal osmotic pressure of plasma became lowered markedly (Fig. 21). Renal circulation

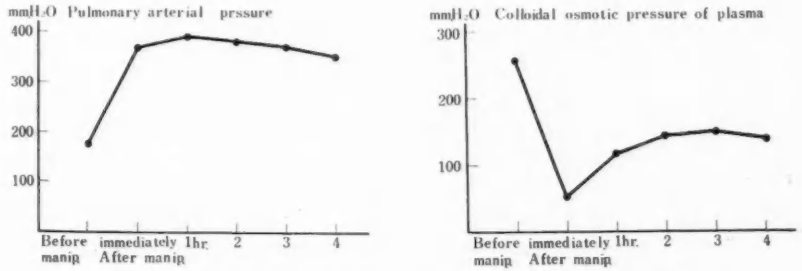


Fig. 21. Changes in pulmonary arterial pressure and colloidal osmotic pressure in the process of pulmonary edema produced by hypoxia, inspiratory resistance and rapid saline infusion after lobectomy.

as well as renal function in the early stage were so good that the infused fluid was completely excreted, but in the late stage the excretion of the fluid became retarded resulting in the retention of both water and electrolytes in the body (Fig. 22). The amount of the tissue fluids became increased in

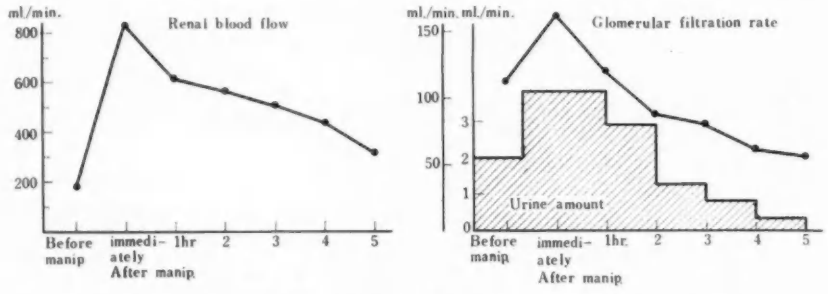


Fig. 22. Changes in renal circulation in the process of pulmonary edema produced by hypoxia, inspiratory resistance and rapid saline infusion after lobectomy.

all the organs, particularly in the lung. There were some increase in the excretion of antidiuretic substance and of adrenocortical hormones, and an increase of ferritin in blood (Fig. 23). There was an increase in the

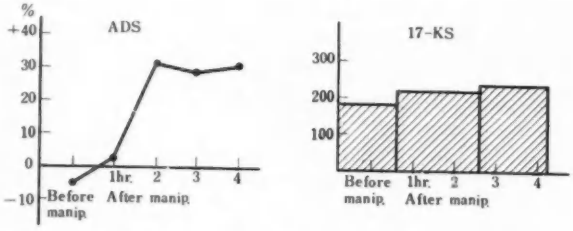


Fig. 23. Endocrine changes in the process of pulmonary edema produced by hypoxia, inspiratory resistance and rapid saline infusion after lobectomy.

activity of fibrinolytic ferment in blood. These changes were not remarkable immediately after the procedures of producing pulmonary edema, but they progressed in intensity gradually in the late stage.

In addition, we were also able to produce another type of the experimental pulmonary edema corresponding to the third group of clinical postoperative pulmonary edema; that occurring after an abdominal operation of cases with metabolic disorder such as hypoalbuminemia, anemia and hepatic or renal disturbance. It was produced by an injection of ANTU.[19] In this condition, the permeability of the pulmonary vessels became increased extraordinarily, and there were little changes in pulmonary circulation, electrolytes in blood and of colloidal osmotic pressure in plasma. The renal blood flow as well as urinary output were decreased.

Discussion

From the results of clinical and experimental examinations in the present study, the pathophysiology and the genesis of the clinical postoperative pulmonary edema are assumed as follows.

In case of an acute pulmonary edema occurring following an operation or a trauma of the brain, the operation or the trauma is directly (primarily) responsible for the rise of pulmonary arterial pressure,[28),30)-32)] the prolongation of pulmonary circulation time and the increase in the permeability of the pulmonary capillaries. This pulmonary hypertension is so high that it overcomes the colloidal osmotic pressure to push the fluids out of the vascular bed into the lung tissue.[33)-35)] This factor would play a major rôle in the production of the pulmonary edema. In addition to causing the pulmonary hypertension, the operation or the trauma directly (primarily) causes the changes in renal[28)] or hepatic circulation and in endocrine regulation, inducing anuria and electrolytes disturbance.[28)] The combination of these accelerates the production of exclusive pulmonary edema. Bilateral preoptic lesions cause a severe respiratory depression accompanied by a lowering of oxygen saturation in arterial blood and respiratory acidosis. A similar depression might be seen not only in the bilateral preoptic lesions, but also in an unilateral preoptic lesion or in a thalamic lesion on both sides of the third ventricle. However, either unilateral preoptic lesion or thalamic lesion would not produce any pulmonary hypertension or pulmonary edema. Therefore, the pulmonary hypertension and the pulmonary edema following an operation or a trauma to the brain can not be regarded as a result from a simple respiratory depression alone,[10),26),27)] but should be regarded as a direct result from the damage of the higher center of the reflex arc, though we do not ignore a fact that the respiratory depression will facilitate the production of the pulmonary edema.[19),36)-39)]

The pulmonary edema occurring after an operation for cardiopulmonary diseases accompanied by pulmonary circulatory disturbances is often caused by a misuse of blood transfusion during and after the operation. In such a case, a continual rise of pulmonary arterial pressure and a marked lowering of colloidal osmotic pressure of plasma are the predominating factors causing the pulmonary edema.[40)-42)] Once the pulmonary edema is induced, it becomes a stress resulting indirectly (secondarily) in a renal circulatory failure, a hormonal disturbance, an increase in the permeability of the pulmonary capillaries and the further promotions of the pulmonary edema. The renal factor is one of the important factors in the occurrence of the pulmonary edema. There is a different behavior of the kindey between the case of postoperative pulmonary edema caused by lesion of the central nervous system and the case of postoperative pulmonary edema

of cardiopulmonary diseases. In the former, the kidney acts dynamically and actively to retain water and electrolytes in the body, while in the latter the kidney is not able to deal with rapidly infused water resulting in a passive retention in the body.[28),42)]

The pulmonary edema occurring after an operation of abdominal diseases accompanied with some metabolic disorders such as hypoproteinemia, anemia, and hepatic or renal disturbance is characteristically caused by a tremendous increase in the permeability of the pulmonary capillaries.[29),43),44)]

As far as the prognosis of the postoperative pulmonary edema is concerned, one can find that some cases of postoperative pulmonary edema respond to the treatment nicely and others progress in its severity in spite of every effort of the treatments. One should consider a fact that there are many cases of pulmonary edema which may not be diagnosed clinically because of a lack of clinical manifestations and in these cases the patients recover from transient edema without any specific treatment. Only the cases associated with severe clinical manifestations of the pulmonary edema may receive the therapy and some may recover from it and some may not. In all types of pulmonary edema, 2 phenomena will develop simultaneously: the transudation of the fluids from the vessel into the alveoli or into the stroma and the reabsorption of the fluids through the lymphatic and the vascular vessels. In the early stage of the pulmonary edema, both phenomena become evident. However, in the late stage the transudation surpasses the reabsorption, resulting in manifestation of the severe pulmonary edema. As long as the reabsorption exists, the pulmonary edema may be reversible. If the pulmonary edema, however, progresses in its severity and continues for some period of time, several factors eventually influence upon the reabsorption, resulting in its marked decrease or disappearance, and lead into an irreversible pulmonary edema.

Summary

(1) By investigating many autopsy cases, it was found that the incidence of combination of the pulmonary edema was high in the cases with central nervous system diseases, particularly in the cases having localized foci in the vicinity of the internal capsule, the lentiform nucleus and the third ventricle.

(2) From the histological viewpoint, an attempt was made to classify the clinical cases of postoperative acute pulmonary edema into 3 groups: (1) that occurring after a brain operation or brain trauma, (2) that occurring after a cardiopulmonary operation of cases with pulmonary circulatory disturbances, (3) that occurring after an abdominal operation of cases with metabolic disorders. It is worthy of note that the incidence of the

postoperative pulmonary edema was significantly high after brain surgery.

(3) In the examination of the pulmonary vascular innervation, the reflex pathway has been clarified and the 2 centers were assumed to be in the reflex arc of the innervation of the pulmonary vessels. The higher center of the reflex arc ascending through the vagus nerve was in the nuclei of the preoptic areas, while the lower center of the reflex arc ascending through the sympathetic or sinus nerve was in the medulla. The authors have also confirmed that the site of cerebral damage in the clinical cases of pulmonary edema, occurring after a brain operation or a brain trauma, had a close relation to either the higher or the lower center of the pulmonary vascular innervation or the both.

(4) The authors have succeeded in the experimental production of the characteristic pulmonary edema of cerebral origin by a complete destruction of the bilateral preoptic areas. Pathophysiology concerning the experimentally produced pulmonary edema has been studied in detail.

(5) Based on the results of both clinical and experimental studies, the pathogenesis of the clinical pulmonary edema occurring after a brain operation or a brain trauma was assumed to be as follows. The operation or trauma was directly responsible for the development of pulmonary hypertension, the prolongation of pulmonary circulation time, and the increase in the permeability of the pulmonary capillaries. At the same time, the operation or the trauma directly caused the changes in renal or hepatic circulation and endocrine regulation, inducing anuria, disturbance of water and electrolytes balances. The combination of these factors accelerated a selective pulmonary edema of an acute type.

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Ventilatory Mechanics in Patients with Cardio-Pulmonary Diseases

Part III. On Pulmonary Fibrosis

Kazuaki SERA, M.D.

Pulmonary function studies have been undertaken on the pulmonary fibrosis as diagnosed clinically with an aid of X-rays. The pulmonary function test was made with special reference to ventilatory mechanics.

Studies were also made by comparing with the case of congestive heart failure previously referred in the Part II and the results obtained have been reported in the present paper.

The pulmonary function examined in clinically diagnosed pulmonary fibrosis has revealed restrictive impairment viewed from ventilatory mechanics, yet it still be complicated with high percentage of the condition of chronic obstructive emphysema. Such a condition of restrictive pulmonary impairment is found to be complicated likewise in the case of congestive heart failure.

A method known as regitine test in pulmonary function test has been adopted as a reliable mean to differentiate pulmonary fibrosis from congestive heart failure by observing changes in pulmonary compliance.

The effect of prednisolone was observed in pulmonary fibrotic cases and its efficiency as the therapeutic agent in resumption of pulmonary function was found.

IT has so far been recognized that pulmonary fibrosis is a condition of an abnormally increased fibrotic connective tissue in the lung. According to Spain,[1] fibrotic transformation arises in pulmonary alveolar membrane, pulmonary interstitial substance, pulmonary vessel, pulmonary bronchial system and pleura.

Richards,[2] on the other hand, divided pulmonary fibrosis into 2 categories, i.e. local and diffuse pulmonary fibrosis: pulmonary infarction, pulmonary atelectasis, pulmonary abscess and radiation pulmonary fibrosis are classified into the former group, while old-aged lung, sarcoidosis and chronic congestive heart failure into the latter.

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These studies were supported by the funds of scientific research work in Japanese Ministry of Education, buying the apparatus of ventilatory mechanics.

It is important for us to clarify the characteristics of pulmonary function in the condition of pulmonary fibrosis in general, because it is the resultant condition subsequent to the various diseases, especially cardio-pulmonary lesion.

In this report, attempts are made to examine pulmonary fibrosis from the aspect of mechanics of breathing, emphasizing "pressure efficiency in respiration" already reported in the previous studies,[3] and to differentiate the pulmonary fibrosis from congestive heart failure, as both conditions present identical results in so far as pulmonary function tests are concerned.

Methods and Materials

As already mentioned, pulmonary fibrosis can be classified into 2 types, i.e. local and diffuse. For the present studies, the author has assumed that the cases of diffuse pulmonary fibrosis will be the choice since the aim of the study is to find pulmonary function as a whole.

The 14 cases chosen were those diagnosed as pulmonary fibrosis, and all of these have presented X-ray findings of pulmonary fibrotic changes. Most of these patients had complaints of dyspnea, but none of them had history of bronchial asthma or pulmonary emphysema characterized by enlarged chest wall. Among them one patient was diagnosed as the case of Hamman-Rich disease verified by biopsy findings. Out of 14 patients, 7 were eliminated from the study because they were found by spirometric tests to be complicated with either obstructive signs or emphysema due to chronic obstruction. The remaining 7 cases have been selected as a group in order to study the true characteristics of pulmonary fibrosis.

In addition, to investigate the general trend of diffuse obstructive emphysema, 7 cases were selected where 6 cases presented the history of bronchial asthma and one chronic bronchitis. These cases were diagnosed on the basis of X-ray findings characterized by either marked descent of diaphragm or clear pulmonary fields, accompanied with enlarged chest wall, and symptoms such as dyspnea after exertion.

In comparison with the above cases, pulmonary function studies were made in 16 cases with congestive heart failure of Class III in classification of New York Heart Association. Moreover, regitine-test in pulmonary function was performed in 5 cases of Class III and 4 cases of Class IV, and additional 9 cases of Class I or II.

For the normal subjects, 7 were chosen in whom no cardio-pulmonary diseases were found by physical examination and chest X-ray film.

Pulmonary function tests were performed on the subjects in supine position. The normal value was estimated by the normal predicted vital capacity value of Baldwin's supine position; maximum breathing capacity was figured out by obtaining the predicted value per body surface area according to the classification of sex and age following Baldwin and others and to the data obtained by means of spirometer in 250 normal subjects who were examined in supine position at rest.

Functional residual capacity was recorded by open circuit method of pure oxygen breathing; and such items as pulmonary compliance, respiratory work and "pressure efficiency in respiration" were obtained by intraesophageal pressure method;[4),5)] effective pulmonary compliance was calculated by average 10 respiratory cycles, while airflow resistance was calculated by 6 to 10 respiratory cycles in average after measuring it by interruption method at the inspiratory mid-point. Pressure-volume curve was drawn by choosing a respiratory cycle in which effective pulmonary compliance and tidal volume showed the nearest value to the mean value of 10 respiratory cycles.

Results

A) Characteristics of Selected Pulmonary Fibrosis.

Among 14 patients in whom diffuse fibrotic process of the lungs was observed on X-ray film, some showed a notable check valve mechanism on Tiffeneau curve, while some showed a remarkable air trapping with Leslie index of more than 5%. Air trapping, strongly suggestive of diffuse obstructive emphysema, was also well demonstrated on the spirogram made for maximum breathing capacity test. Hence, pulmonary fibrotic cases which were thought to be complicated with emphysema due to chronic obstructive nature had to be eliminated. Thus 7 cases were selected out of 14 patients. It is true high percentage of pulmonary fibrosis cases are complicated with the condition of emphysema due to chronic obstruction and the fibrosis of small bronchial tree seemed to be the main factor.

Table I. Ventilatory Mechanics in Patients with Pulmonary Fibrosis, Pulmonary Emphysema and Congestive Heart Failure Class III

	Pulmonary fibrosis		Congestive heart failure Class III	Normal	Pulmonary emphysema
	Selected cases (6 cases)	(12 cases)	(12 cases)	(7 cases)	(6 cases)
Respiratory rate (per minute)	24.0 14.7~34.0	21.6 8.2~34.0	17.1 9.7~31.7	17.4 14.0~21.0	21.0 13.3~27.0
Respiratory work (Kg·M./min.)	0.372 0.138~0.663	0.245 0.090~0.663	0.271 0.091~0.492	0.036 0.027~0.050	0.502 0.109~1.292
Respiratory work (Gm·cm./100 ml.vent.)	419 242~592	364 83~592	329 173~605	73 49~109	435 71~639
Pressure efficiency in respiration	0.02 −0.51~0.43	−0.35 −1.05~0.60	0.26 −0.14~0.62	0.56 0.41~0.71	−1.16 −2.44~0.56
Effective compliance (L./cm.H_2O)	0.107 0.060~0.168	0.219 0.060~0.328	0.085 0.052~0.116	0.180 0.156~0.190	0.283 0.110~0.416
Static compliance (L./cm.H_2O)	0.099 0.060~0.177	0.466 0.060~1.620	—	0.185 0.167~0.193	0.535 0.320~0.852
Respiratory flow resistance (inspiratory mid-point) (cm.H_2O/L./sec.)	3.79 2.81~5.81	5.44 1.48~7.74	3.41 2.13~4.17	2.16 1.55~2.57	7.54 2.48~21.10

As shown in Table I, "pressure efficiency in respiration" of the selected cases showed lower value than normal, while "pressure efficiency in respiration" of the other group of patients who were diagnosed as pulmonary fibrosis showed the sharp descent. As for the respiratory work, both selected group and the remainder revealed the value over normal value; however, in effective and static pulmonary compliance, the selected group showed characteristic low value than the normal though some of the non-

Table II. Pulmonary Function Studies in Patients with Pulmonary Fibrosis, Pulmonary Emphysema and Congestive Heart Failure Class III

	Pulmonary fibrosis		Congestive heart failure Class III	Normal	Pulmonary emphysema
	Selected cases (7 cases)	(14 cases)	(16 cases)	(7 cases)	(7 cases)
% of V.C.	63.4 (37.2~122.2)	53.4 (34.8~122.2)	66.4 (47.8~108.8)	100.2 (80.0~120.7)	59.2 (46.7~97.5)
% of T.L.C.	87.2 (64.8~137.8)	75.1 (47.6~137.8)	87.7 (59.7~119.6)	101.3 (98.0~109.7)	110.0 (88.4~136.7)
RV/TLC×100	48.1 (38.7~65.8)	48.3 (30.8~72.4)	43.9 (30.6~64.1)	23.7 (17.0~30.8)	61.1 (45.4~68.2)
f/min.	25.7 (14.7~34.4)	20.5 (8.2~34.4)	17.1 (9.7~31.7)	17.4 (14.0~21.0)	20.4 (13.3~25.7)
V_T (ml.)	394 (282~687)	451 (282~819)	421 (322~631)	525 (481~556)	477 (381~819)
M.V. (L./M.^{2}(B.S.A.))	5.77 (4.07~7.15)	5.80 (4.07~9.78)	4.88 (3.23~6.74)	5.46 (3.97~7.71)	6.55 (4.87~10.36)
Vent. equivalent	4.19 (3.28~5.39)	4.16 (2.56~5.39)	3.60 (2.7~5.6)	3.74 (2.38~5.09)	4.45 (2.70~6.54)
% of M.B.C.	60.3 (28.1~72.2)	50.3 (26.8~90.4)	65.9 (32.2~126.3)	113.1 (74.0~135.2)	37.5 (11.7~53.4)
A.V.I.	0.97 (0.76~1.78)	0.85 (0.54~1.78)	1.00 (0.43~1.76)	1.13 (0.93~1.33)	0.63 (0.45~0.86)
B.R.R. (%)	82.1 (73.1~91.5)	80.1 (68.1~94.4)	83.5 (73.3~92.7)	93.8 (90.0~95.3)	68.7 (54.1~84.5)
T.V.C. (1 sec.%)	63.8 (46.2~76.5)	54.9 (38.7~80.7)	61.3 (49.6~83.4)	81.8 (77.4~84.4)	42.4 (27.3~55.9)
T.V.C. (3 sec.%)	78.7 (61.6~91.3)	72.6 (59.3~91.3)	83.9 (68.9~100.0)	94.8 (85.8~100.0)	69.5 (43.0~80.5)
N_2 clearance (7 min.%)	1.2 (0.3~2.0)	1.9 (0.3~4.7)	1.0 (0.3~2.4)	0.9 (0.4~1.3)	5.1 (2.0~7.5)
Peripheral arterial blood SaO_2 (%)	91.4 (82.4~96.1)	93.1 (82.4~98.1)	94.5 (87.3~99.0)	96.9 (91.2~100.0)	91.5 (85.7~95.3)
Peripheral arterial blood Pco_2 (mm.Hg)	35.7 (30.1~44.0)	37.8 (30.1~50.5)	38.1 (28.0~49.0)	36.5 (28.0~45.0)	48.1 (41.0~51.4)
Peripheral arterial blood pH	7.42 (7.38~7.49)	7.41 (7.38~7.49)	7.40 (7.31~7.43)	7.40 (7.38~7.45)	7.40 (7.30~7.51)
C.T.I.	0.54 (0.44~0.65)	0.50 (0.41~0.65)	0.72 (0.62~0.86)	0.51 (0.42~0.54)	0.48 (0.38~0.54)

Note: (~) show ranges, C.T.I. is cardio-thoracic index.

selected with pulmonary fibrosis either high or low values. Air flow resistance of the selected cases showed slight increase, recording 3.79± 0.59 cm. H_2O/L./sec., while among non-selected pulmonary fibrosis, some had higher value as in emphysema. The results obtained by pulmonary function test are shown in Table II.

B) Contrast with Diffuse Obstructive Pulmonary Emphysema.

Comparing chronic diffuse obstructive pulmonary emphysema with the selected cases of pulmonary fibrosis, as shown in Table I, there was a common decline of "pressure efficiency in respiration" associated with increased respiratory work, however, definite difference was observed with regard to pulmonary compliance and air flow resistance. In pulmonary emphysema, notable increase was shown in air flow resistance as well as elevation of static pulmonary compliance, but in the selected cases of pulmonary fibrosis, static and effective pulmonary compliance declined and air flow resistance increased to a small extent. In the field of common pulmonary function test, Pco_2 of peripheral arterial blood increased in pulmonary emphysema, while that of the selected cases was rather lower than the normal subjects. Although it is commonly accepted that pulmonary N_2 emptying rate shows high value in pulmonary emphysema, the selected cases were nearly in the same value as

Table III. Characteristic Feature in Pulmonary Function Studies in Patients with Pulmonary Congestion, Pulmonary Fibrosis and Pulmonary Emphysema

		Congestive heart failure Class III	Pulmonary fibrosis selected cases	Pulmonary emphysema
Volumetry	% of V.C.	⇩	⇩	⇩
	% of T.L.C.	⇩ or Normal	⇩ or Normal	⇧ or Normal
	R.V./T.L.C. × 100	⇧	⇧	⇧⇧
	N_2 clearance (7 min.)	⇩ or Normal	⇩ or Normal	⇧⇧
Ventilatory equivalent		⇧	⇧	⇧
Arterial blood	SaO_2 %	⇩	⇩	⇩
	Pco_2 mm.Hg.	⇩ or Normal	⇩ or Normal	⇧⇧
Ventilatory mechanics	Timed V.C. (1 sec.%)	⇩ or Normal	⇩ or Normal	⇩⇩
	Air velocity index	Normal	Normal	⇩⇩
	Static compliance	⇩	⇩	⇧ or Normal
	Respiratory flow resist.	⇧	⇧	⇧⇧
	Respiratory work	⇧⇧	⇧⇧	⇧⇧
	Pressure efficiency	⇩	⇩	⇩⇩
Cardio-thoracic index		⇧⇧	⇧ or Normal	⇩ or Normal

the normal subjects. Air velocity index of pulmonary emphysema was considerably low (0.63 (range 0.45–0.86)), while the selected cases showed nearly the normal value (0.97 (range 0.76–1.78)) and timed vital capacity was low in both of these groups, especially in the former. In the selected cases, the percentage of residual volume per total lung capacity was 46.1% on an average, while in the cases of pulmonary emphysema, it was 61.1% on an average. Thus the selected cases of pulmonary fibrosis still showed considerably high value in residual volume percentage though it was low than that of emphysema. Other data are as shown in Table II.

C) Difference between Congestive Heart Failure and Pulmonary Fibrosis.

The results in congestive heart failure has been reported in part II.[7] With reference to difference and similarity among congestive heart failure of Class III, the selected cases of pulmonary fibrosis and chronic diffuse obstructive emphysema were studied. As shown in Table III, the results in congestive heart failure is quite different from those in chronic obstructive emphysema, but identical with those in the selected pulmonary fibrosis. That is to say, congestive heart failure is likely to develop pulmonary compliance as we find in pulmonary fibrosis and differentiation is hardly possible with pulmonary function tests that we use, i.e. measurement of pulmonary compliance, air flow resistance, respiratory work and "pressure efficiency in respiration". Although clinical signs, X-ray findings and electrocardiogram are the possible means of differentiation, the author had attempted the method of differentiation by relying on functional test.

D) Differential Diagnosis between Pulmonary Fibrosis and Pulmonary Congestion by Administration of Regitine.

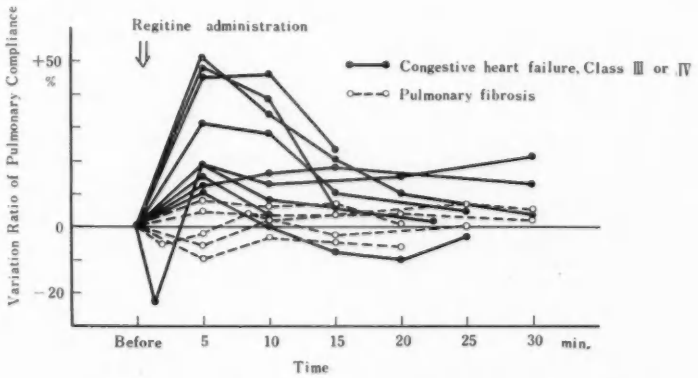

Fig. 1. Effective compliance changes in patients with congestive heart failure and pulmonary fibrosis following intravenous injection of regitine.

Table IV. Changes in Pulmonary Function by Prednisolone Treatment in Three Patients with Pulmonary Fibrosis

		Before		After		After−Before/Before	
	Name	Cases	Mean	Cases	Mean	Cases	Mean
% of vital capacity (%)	A. M.	56.9	53.9	86.1	72.9	+0.51	+0.33
	T. N.	41.7		58.0		+0.39	
	K. I.	63.0		73.6		+0.17	
% of total lung capacity (%)	A. M.	75.3	67.5	96.9	86.9	+0.29	+0.29
	T. N.	47.6		80.7		+0.70	
	K. I.	79.6		83.0		+0.04	
RV/TLC×100 (%)	A. M.	47.6	37.7	38.7	45.5	+0.19	+0.21
	T. N.	39.5		50.3		+0.27	
	K. I.	36.0		47.6		+0.32	
Minute volume/B.S.A. (L./min./M.²)	A. M.	6.40	6.31	4.07	5.29	−0.36	−0.16
	T. N.	6.30		5.84		−0.04	
	K. I.	6.22		5.96		−0.04	
O_2 consumption (ml./min./M.²(B.S.A.)	A. M.	119.0	136.1	107.4	119.1	−0.10	+0.12
	T. N.	153.3		123.0		−0.20	
	K. I.	136.0		127.0		−0.07	
% of maximum breathing capacity (%)	A. M.	61.5	48.8	69.5	59.7	+0.13	+0.22
	T. N.	31.2		49.0		+0.57	
	K. I.	53.7		60.6		+0.13	
Air velocity index	A. M.	1.08	0.90	0.81	0.83	−0.25	−0.08
	T. N.	0.75		0.85		+0.13	
	K. I.	0.85		0.82		−0.04	
1 sec. timed vital capacity/V.C.×100 (%)	A. M.	46.2	46.5	45.7	47.9	−0.01	+0.03
	T. N.	48.3		48.4		0.00	
	K. I.	45.0		49.5		+0.10	
Peripheral arterial blood SaO_2 (%)	A. M.	93.6	92.5	96.1	97.3	+0.03	+0.05
	T. N.	90.8		98.9		+0.09	
	K. I.	93.2		96.8		+0.04	
Peripheral arterial blood Pco_2 (mm.Hg)	A. M.	35.5	42.7	34.5	35.0	−0.03	−0.18
	T. N.	50.5		38.4		−0.24	
	K. I.	42.2		32.2		−0.24	
Effective compliance ($L./cm.H_2O$)	A. M.	0.064	0.115	0.168	0.147	+1.63	+0.28
	T. N.	0.062		0.058		−0.07	
	K. I.	0.215		0.218		+0.01	
Air flow resistance inspiratory mid-point ($cm.H_2O/L./sec.$)	A. M.	5.06	5.29	4.22	5.49	−0.17	+0.04
	T. N.	4.05		4.83		+0.19	
	K. I.	6.77		7.44		+0.10	
Respiratory work (Gm·cm./100 ml.vent.)	A. M.	365	547	242	251	−0.34	−0.54
	T. N.	500		268		−0.47	
	K. I.	777		244		−0.69	
Pressure efficiency in respiration	A. M.	0.38	−0.19	0.43	0.40	After−Before 0.05	After−Before 0.59
	T. N.	−0.36		0.41		0.77	
	K. I.	−0.50		0.37		0.87	

As shown in Fig. 1, an investigation was undertaken to differentiate pulmonary fibrosis from pulmonary congestion due to heart failure by variation ratio of pulmonary compliance before and after the injection of regitine 5 to 10 mg. intravenously. In congestive heart failure of Class III and IV in classification of New York Heart Association, the response was most remarkable, however, in pulmonary fibrosis, the variation was hardly noticeable, and if there is any, it was less than 10 percent. On the other hand, the variation in 9 cases of Class I and Class II showed no more difference than that of pulmonary fibrosis (not included in Fig. 1). As to pulmonary compliance variation, the highest value was reached within 3 to 10 minutes. Thus, the pulmonary congestion can be predicted by comparing the values before and 5 minutes after the administration of regitine. The same can be said of "pressure efficiency in respiration". "Regitine test" which is proposed by the author is, therefore, an useful way to detect pulmonary congestion.

E) Effect of Administration of Prednisolone in the Patient with Pulmonary Fibrosis.

An investigation was made by comparing the pulmonary function before and after the administration of prednisolone 5 to 30 mg. a day in 3 cases of pulmonary fibrosis for 3 weeks up to 3 months. The results revealed that there were an increased vital capacity and total lung capacity, an elevated peripheral arterial blood O_2 saturation and pulmonary compliance, and a decrease in percentage of residual volume per total lung capacity and respiratory work as shown in Table IV. Concerning "pressure efficiency in respiration", it increased much higher, while air flow resistance, air velocity index and percentage of one second timed vital capacity per inspiratory slow vital capacity remained unchanged.

Discussion

Insomuch as increase in percentage of residual volume per total lung capacity be defined as pulmonary emphysema as Motley[8] did, the pulmonary fibrosis should be classifiable under this heading. Mitchell[9] stated that such pulmonary fibrosis as silicosis, sarcoidosis and Hamman-Rich disease have been labeled as pulmonary emphysema; however, taking the matter into consideration from the view point of ventilatory mechanics, pulmonary fibrosis is entirely different from diffuse chronic obstructive emphysema, and it should probably be defined as the "disease with substantial restrictive impairment." In pulmonary emphysema in these instances, it has been presumed that the tissue would undergo typical pathological changes. And pulmonary fibrosis is often accompanied by emphysematous changes as presented previously, besides bronchiolar fibrosis may induce obstructive signs. Hence, it

should not be proper to regard all cases with a sign of obstructive disturbances as chronic obstructive emphysema. The entity of chronic diffuse obstructive emphysema should be interpreted to be characterized by a triad consisting of elevated static pulmonary compliance, advent of check valve mechanism and air-trapping from the aspect of ventilatory mechanics.

On the other hand, it has already been stated in Part II that the restrictive impairment is commonly found in either congestive heart failure or pulmonary fibrosis and that the progress of congestive heart failure implies the advancing restrictive impairment. For the differential diagnosis, the administration of regitine has so far been proved to be the most effective procedure although the other methods such as postural change, application of the leg binder to relieve congestion and administration of morphine or cardio-diuretics will be reported later. The regitine test in pulmonary function also serves as a reliable approach to confirm the clinical diagnosis of pulmonary congestion.

With reference to the administration of prednisolone, 2 cases out of the 3 have proved its efficiency in improving pulmonary function, indicating the fact that at least a part of pulmonary fibrosis seems to resume pulmonary function. Treatment of Hamman-Rich disease with the administration of prednisolone has been reported by many[10),11)] with marked improvement in dyspnea and in chest X-ray films, but efficacy of the drug could not be substantiated in the present study, since biopsy has not been attempted to diagnose Hamman-Rich disease.

Conclusion

(1) With the purpose of studying the ventilatory mechanics in pulmonary fibrosis, the author had selected 14 cases which were clinically diagnosed as diffuse fibrosis of the lungs and were confirmed with chest X-ray films. Out of 14, 7 cases which presented no complication were used in the present study as the selected cases of pulmonary fibrosis. The other 7 complicated cases were those developing chronic obstructive pulmonary emphysema with definite signs of check valve mechanism and air trapping. Comparative studies were made among pulmonary emphysema, congestive heart failure and these selected cases of pulmonary fibrosis. It has been found that the cases presented invariably showed restrictive pulmonary impairment just as those with pulmonary congestion.

(2) The variation of pulmonary compliance has been regularly observed upon the administration of regitine to these cases of pulmonary fibrosis and congestive heart failure. The more advanced the heart failure, the more variable pulmonary compliance. Regitine test in pulmonary function which is named by the author can be used for the diagnosis of pulmonary congestion.

(3) Prolonged administration of prednisolone seemed to have resulted in a marked improvement of pulmonary function. Especially it has been elucidated that pulmonary fibrosis is reversible by the elevation of pulmonary compliance and "pressure efficiency in respiration."

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Air Pollution Asthmatic-Bronchitis among United States Personnel in Japan*

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Asthmatic bronchitis, presumably due to air pollution, has been a major case of sickness among U. S. forces personnel in the Tokyo-Yokohama area since 1946. The most prominent symptoms are nocturnal cough, wheezing, and shortness of breath in an individual who has a negative history of asthma prior to coming to Japan. The attacks of coughing and wheezing occur most frequently at night and during periods of increased smog concentration.

Perhaps most characteristics of this disease is the marked subsidence of symptoms when the patient leaves the Kanto Plain. Our treatment has been outlined with special emphasis on bronchodilators, hydration, and liquefaction of bronchial secretions. Adrenal steroids are used in the seriously ill patient and has been very useful in relieving symptoms. Patients with marked shortness of breath, with airflow obstruction by pulmonary function studies and with frequent occurrence of coughing and wheezing are usually set back to the United States. Follow-up studies show that almost all of these patients dramatically improved as soon as they are sent back to the United States.

HUBER et al. reported in November 1954 a new environmental respiratory disease which at that time was popularly termed "Yokohama Asthma."[1] According to that report the disease was first recorded in 1946 at the U.S. Army Hospital, Yokohama, Japan, where clinicians recorded an unusually large number of patients with asthma.

The 1951 Annual Historical Report of the 406 Medical General Laboratory in Japan stated that a respiratory disease whose symptoms ranged from mild bronchial irritation to severe respiratory distress, often requiring emergency treatment and hospitalization, was becoming increasingly more prevalent. It was no longer confined to the Yokohama area but involved the entire Kanto Plain.[2] This disease was characterized by attacks beginning in the evening or early morning hours, and was usually accompanied by severe coughing, wheezing, and shortness of breath. It was noted that Yokohama, with its high industrialization and its location on a bay enclosed

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by hills and bluffs, offered ideal conditions for smog formation and retention.

With the increased smog concentration, there was a definite increase in the attack rate. It was also observed that patients obtained prompt relief when moved for even short distances from this region. It has been a common observation in the Kanto Plain that the incidence of this disease is greater in dry winter months when there is increased smog concentration. This disease seems to begin in late September and increases in the winter months. It starts to decline in March and is almost absent in the summer months.

We at the U. S. Army Hospital, Camp Zama, are reasonably convinced that this disease is due to industrial air pollution. Smog appears to be increasing in concentration and frequency with the increased industrial expansion in this area (Kanto Plain). This conclusion is supported by the common observation that flying personnel with this disease get dramatic relief upon reaching altitudes of 5 thousand feet above their Kanto Plain base. Also many patients obtain relief by going to the mountain resorts outside the Kanto Plain. These patients develop shortness of breath again on returning to their Kanto Plain home.

This asthmatic disease is characterized by coughing, wheezing, and shortness of breath. It occurs in normal health individuals who usually do not have a past history of asthma or other allergy states prior to their arrival in Japan. The typical history of these patients begins with coughing, usually at night or in the early morning hours. Their length of stay in the Kanto Plain before onset of symptoms varies from 2 weeks to several years. The patient is often seen for the first time complaining of having coughed most of night for several nights. The physical examination at this stage is often completely negative. The patient is usually given a cough mixture and at times a broad spectrum antibiotic, which may or may not give relief. A few weeks later with wheezing and marked shortness of breath, he is seen at night as an emergency. At this time he is treated with epinephrine or intravenous aminophylline with some symptomatic improvement. The response to this emergency treatment is not as dramatic as in the usual case of bronchial asthma. From this time on the patient is seen with increasing frequency in our medical clinics. He may have several hospital admissions and at times he may be critically ill.

The most significant characteristic of this disease is the patient's becoming entirely asymptomatic after departure from the Kanto Plain.

The patient first seeks medical attention for chronic loss of sleep due to noctural coughing and wheezing. It is only after careful questioning by the physician that patient reveals his severe limitation of physical activity because of shortness of breath. He tends to avoid physical

exertion. This shortness of breath is so insidious that the patient is rarely aware of his inability to perform sustained physical exertion. As was mentioned above, the physical examination is usually negative except in the acute attack. We have noticed one finding that was fairly constant. If the patient takes in a deep breath and forcible exhales, expiratory wheezes can be heard. Extensive laboratory studies offer little guidance in treating the patient in an acute attack. The sputum, though it may appear purulent, on culture unually fails to reveal any significant pathogenic organisms. The chest x-rays, except in a few instances, are within normal limits. Sputum smears occasionally show eosinophile; however, this is not a constant finding. Blood eosinophilia is not a constant finding.

Because the physical examination and laboratory studies did not greatly assist us in determining the severity of the patient's disease, we decided to do pulmonary function studies. We needed some objective method that would be permanently recorded. This would allow us to make future tests and make comparisons. We could determine the severity

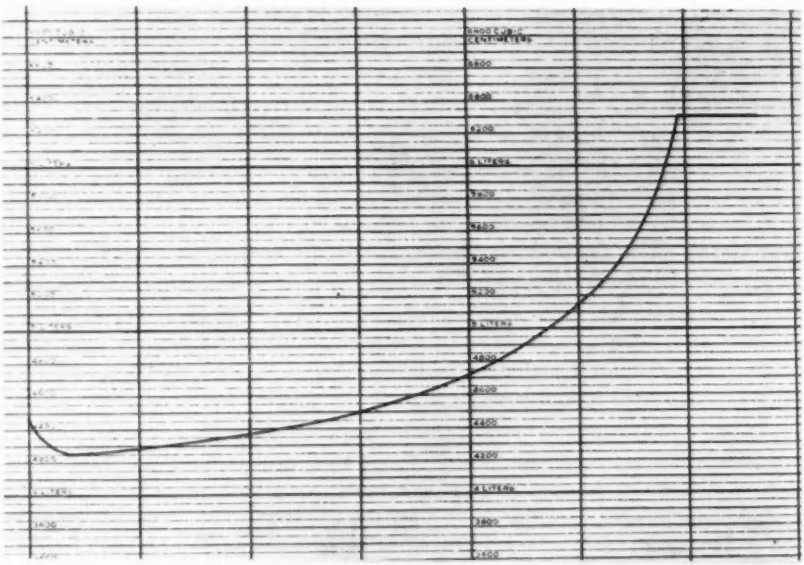

Fig. 1-A. D.R., a 30 year-old white male who developed coughing and wheezing shortly after arriving in Japan. He became progressively worse and was hospitalized. On continuous medication, he showed only slight improvement. He continued to be markedly short of breath. The above spirogram was taken just prior to his return to the United States. Note the marked air flow obstruction. Vital capacity 4,343 ml. or 99.4% of predicted, 1 second vital capacity 2,679 ml. or 61.8%, MMEF 1.38 L./sec., MET 1.56 seconds MBC 113.3 L./min. or 72.5% of predicted.

of the patient's disease and detect progression of the disease. We acquired a 13.5 liter Benedict-Roth respirometer with 2 speeds. One speed was 160 mm. per minute which was suitable for doing Maximum Breathing Capacities (MBC). The other speed of 32 mm. per second was necessary to produce a Spirogram from which flow rates could be measured.[3] The flow rates consisted of one-second vital capacity, maximum mid-expiratory flow (MMEF), and mid-expiratory time (MET).[4] These studies provided a fairly reliable index as to the patient's response to treatment and determination of the amount of disability which the patient had between attacks (Fig. 1). Most of the patients had evidence of marked air flow obstruction even between attacks and on medication. Of great interest, none of these patients showed improvement of their functions after intermittent positive pressure breathing (IPPB) using Isuprel or epinephrine.

Between January 1960 and April 1960 over 100 patients with this disease were evaluated at our hospital. Of this number, 11 patients were returned to the United States. Of the 11 patients who were sent to the

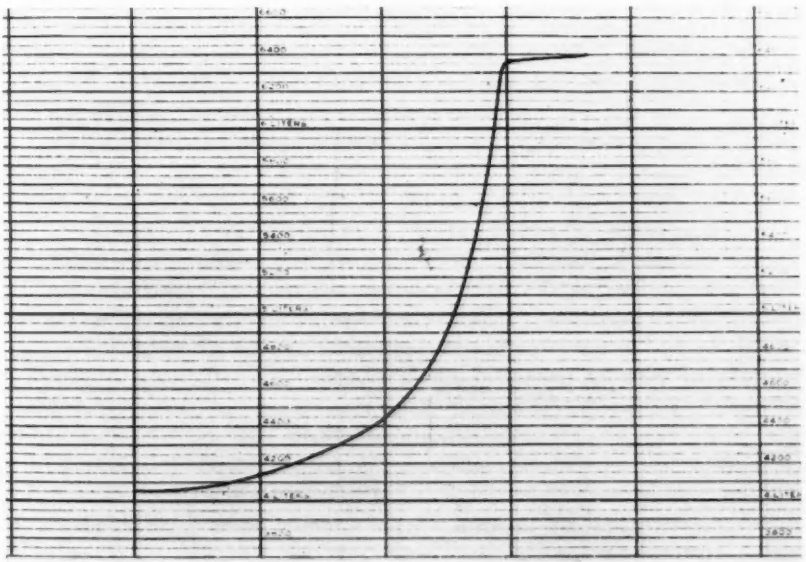

Fig. 1-B. Spirometric tracing taken three weeks after arrival in Continental United States. Patient was on no medication after evacuation.

Note the marked improvement in the air flow. Vital capacity 5,007 ml. or 116% of predicted, 1 second vital capacity 4,195 ml. or 83.5%, MMEF 4.33 L./sec., MET 0.56 seconds, MBC 193.6 L./min. or 124.2% of predicted.

United States, we received studies done in the United States on 8 patients. The results of these studies are as follows:

	11 patients sent to the United States	8 patients who had evaluations done after arrival in the United States
	Mean values	Mean values
Vital capacity (VC)	4,220 ml.	4,462 ml.
Predicted VC	3,965 ml.	4,307 ml.
% of pred. VC	106.5%	104.0%
1 second VC	2,485 ml.	3,488 ml.
% 1 second VC of VC	59%	78.2%
MMEF*	1.95 L./sec.	3.05 L./sec.
MET**	1.60 sec.	0.83 sec.
MBC	106.5 L./min.	169 L./min.
Predicted MBC	144 L./min.	143.8 L./min.
% of predicted MBC	73.4%	117%

The results of these studies show the dramatic improvement after the patients returned to the United States. It is of significance that few if any of the patients had changes in their Vital Capacities. None of these patients had a past history of asthma before coming to Japan.

Treatment

Our treatment of severe cases of air pollution asthma consists of the following: (1) Placing the patient in an oxygen tent with added moisture supplied by nebulization. (2) Giving Aminophylline up to 1 Gm. per 1,000 ml. in 5% dextrose and water intravenously which produces bronchodilation and aids in liquefaction of sputum by hydration. (3) Giving saturated solution of potassium iodide in doses of 15 drops, 3 or 4 times daily. In severe cases with thick tenacious sputum, this may be increased to 10 drops every two hours until an effect is produced. (4) Administering Isuprel, $^1/_2$ ml. of a 1–200 solution, with $1^1/_2$ ml. of saline by a nebulizer energized by oxygen, repeated every three or four hours. (5) Using Tetracycline in patients with purulent sputum. This may be modified by subsequent bacteriological studies. Neomycin, 50 mg., added to the Isuprel nebulization may help to clear the purulent sputum more rapidly. (6) Avoiding sedation if possible. The use of small amounts of Demerol may be helpful, although contraindicated in severe hypoxia. (7)

* MMEF in these individuals should be 3 L./sec. or more.

** MET in these individuals should be less than 0.80 sec.

Using Codeine only when the cough exhausts the patient. (8) Giving Epinephrine 0.3 to 0.5 ml. of a 1–1,000 solution, subcutaneously every two hours. (9) Accomplishing hydration by parenteral and oral fluids. (10) ACTH, or adrenal steroids, are indicated in critically ill patients or those having an unsatisfactory response to intensive treatment outlined above.

Cases not requiring hospitalization seem best controlled by oral Ephedrine-containing preparations and Isuprel by hand nebulizer.

Summary

Asthmatic-bronchitis, presumably due to air pollution, has been a major cause of sickness among U. S. Forces personnel in the Tokyo-Yokohama area. The most prominent symptoms are nocturnal cough, wheezing, and shortness of breath. The disease seems to differ from typical bronchial asthma in the following ways: (1) Onset in early adult life. (2) Absence of allergy history. (3) Persistent shortness of breath between attacks. (4) Persistent abnormal pulmonary function tests between attacks. (5) Resistance to treatment early in the course of the disease. (6) No improvement of pulmonary function studies after Intermittent Positive Pressure Breathing (IPPB) using Isuprel or epinephrine.

Perhaps most characteristic of this disease is the marked subsidence of symptoms when the patient leaves the Kanto Plain. Treatment has been outlined with special emphasis on bronchodilators, hydration, and liquefaction of bronchial secretions. Steroids are used in the seriously ill patient, but they do not completely relieve him of exertional dyspnea. Patients with marked shortness of breath with air flow obstruction by pulmonary function studies and with frequent occurrence of coughing and wheezing, should not be maintained on long-term steroids but should move out of the Kanto Plain. A simple test would be to have the patient go for a few days out of the Kanto Plain and see if he gets relief of his symptoms. If he does get relief, then he should consider moving.

It is reasonable to assume that, with increasing industrialization in the Kanto Plain and accompanying increased air pollution, the incidence rate of this disease will increase. With increased smog in other areas of the world, it may be that this disease will be found elsewhere.

Acknowledgment

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Superior Vena Cava-Pulmonary Artery Anastomosis, Its Experimental Study and Clinical Applications

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Recently the partial right heart bypass by means of superior vena cava-right pulmonary artery anastomosis has been studied as a therapeutic method for some congenital heart diseases and even a few case reports with success have been carried out. But, because animal experiments had demonstrated high mortality and frequent postoperative complication of chylothorax, the authors originally established the procedure to perform safely on clinical cases and to prevent the postoperative complication of chylothorax, and performed the superior vena cava-right pulmonary artery anastomosis based upon this procedure on 4 clinical cases.

RECENTLY the superior vena cava-pulmonary artery anastomosis is being tried for some congenital cyanotic heart diseases. It has already been demonstrated in animal experiments by Glenn et al.[1),2)] and Robicsek et al.[3)] that the superior vena caval blood could be perfused into the pulmonary artery without the right heart function if the pulmonary artery resistance was within normal. Therefore this anastomosis may be indicated for surgical palliation of some congenital cyanotic diseases with reduced pulmonary flow and low pulmonary atery resistance which are still difficult to be corrected anatomically. Although the Blalock-Taussig operation or the aorticopulmonary anastomosis has been previously tried on some of these lesions such as tricuspid atresia and transposition of great vessels, the operative results have been unsatisfactory.

Since the SVC–PA anastomosis raises the arterial O_2 saturation by decreasing the amount of right to left shunt without overloading the left heart, it may be considered that the therapeutic significance of this method is greater than that of Blalock-Taussig operation or the aorticopulmonary anastomosis in which an overload of the left heart may be seen postoperatively.

The purposes of this article is to emphasize some practical yet important problems upon the clinical application of SVC–PA anastomosis which has not been thoroughly evaluated up to the present time, and to

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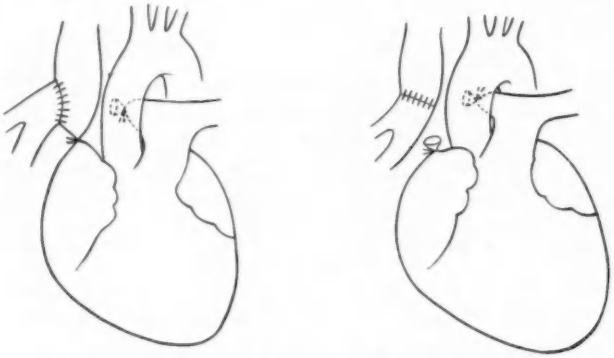
report successfully operated cases of tricuspid atresia, single ventricle and Fallot's pentalogy by this anastomosis.

Experimental Methods

Fifty-three mongrel dogs each weighing from 9 to 17 Kg. were anesthetized by an intravenous injection of veterinary Nembutal (25 mg./Kg.), and an intermittent positive pressure inspiration was used with oxygen. The right fourth intercostal space was opened and the right pulmonary artery was exposed near by the bifurcation of the pulmonary artery. The superior vena cava was also exposed from its atrial junction to the innominate veins and the azygos vein was severed between double ligatures.

Two types of anastomosis were performed.

Group I—In 33 dogs, the superior vena cava-right pulmonary artery anastomosis (SVC-RPA anastomosis) was carried out in a fashion of side-to-end anastomosis and the proximal portion of SVC was ligated (Fig. 1).



Side-to-end anastomosis 33 dogs

End-to-end anastomosis 20 dogs

Fig. 1. SVC-RPA anastomosis.

Group II—In the other 20 dogs, the anastomosis was performed in a fashion of end-to-end anastomosis after SVC was severed near the right atrium (Fig. 1).

In 14 dogs the thoracic duct was ligated during the operation regardless the the types of anastomosis used.

With a use of hydromanometer the jugular venous pressure was measured immediately after the closure of the chest and thereafter once a week postoperatively under a light anesthesia. The thoracocentesis was performed when it was necessary.

Angiograms of SVC-RPA using 76% Urografin were taken in 5 dogs at various postoperative stages.

Macro- and microscopic examination were carried out on both expired and sacrificed dogs.

Experimental Results

1. Early deaths—Early deaths within 48 hours after the operation occurred in 5 dogs in both group I and group II. However, no obstructive thrombus or the rupture of stoma was demonstrated in these dogs. The mortality rates of group I and group II were 15.2% and 25% respectively, indicating a significantly high mortality rate in the group II (Table I).

Table I.

	SVC-RPA anastomosis	
	side-to-end (%)	end-to-end (%)
Number of dogs	33	20
Early deaths	5 (15.2%)	5 (25%)
Occurrence of chylothorax	17 (51.5%)	11 (55%)

2. Chylothorax as postoperative complication—Postoperative chylothorax occurred in 18 dogs of group I and in 10 dogs of group II. This usually occurred within 1 or 2 weeks after the operation. The rates of this complication were 54.5% in group I and 50% in group II, and were not related to the types of anastomosis. In spite of frequent thoracocentesis, all but 3 dogs with complication died from emaciation (Table I.). The ligation of thoracic duct did not show any difference in protective effect from development of chylothorax (Table II).

Table II. Protective Effect of Ligature of Thoracic Duct upon Postoperative Chylothorax

	Thoracic duct ligated	Thoracic duct not ligated
Chylothorax (+)	11	17
Chylothorax (−)	3	12
Total	14	29

Note: Early deaths were excluded.

3. Measurement of postoperative jugular venous pressure—Jugular venous pressure was measured especially in connection with occurrence of chylothorax. Although exact estimation of mid-operative pressure was difficult

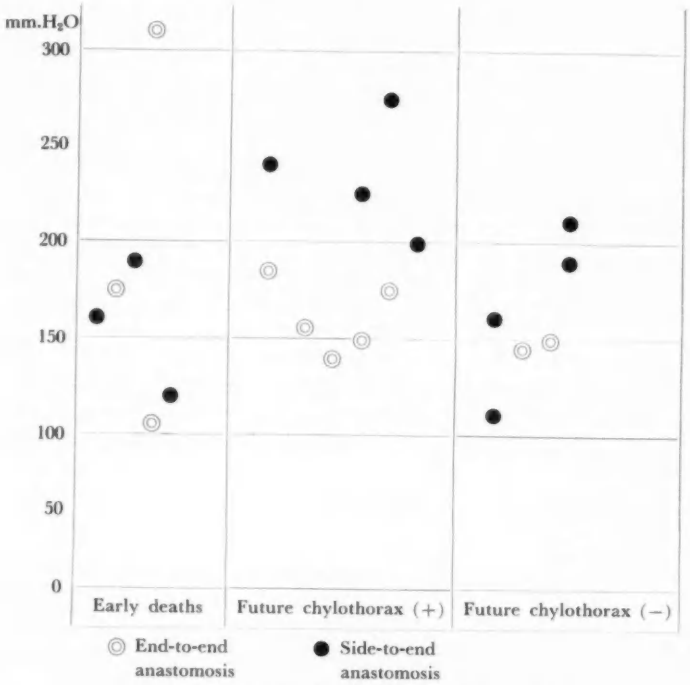
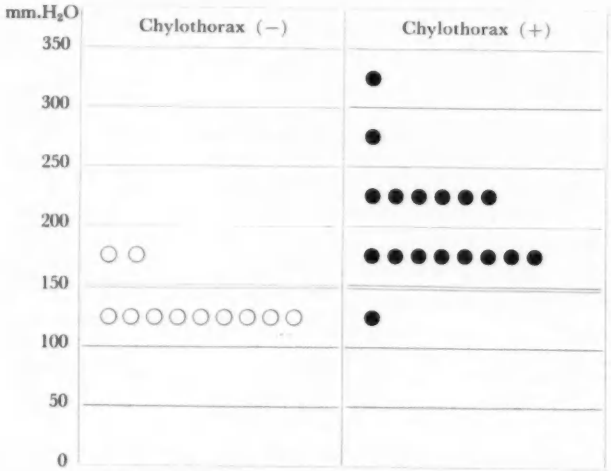


Fig. 2. SVC pressure immediately after operation.



Pressure measurement was carried out at the external jugular vein 1~2 weeks after the operation.

Fig. 3. Relation between SVC pressure and occurrence of chylothorax.

due to influences of anesthesia, changes in blood pressures etc., there was a tendency that the dogs with high venous pressure (over 200 mm.H_2O) were ready to have a complication of postoperative chylothorax (Fig. 2). On the other hand, analyzing jugular venous pressures at the postoperatively stabilized state, a definite correlation was found between the postoperative chylothorax and the pressure over 150 mm.H_2O. The type of anastomosis seemed to have no connection with this correlation (Fig. 3).

4. Observations on expired and sacrificed dogs—Dogs with chylothorax showed an accumulation of chylous fluid of several hundreds ml. mainly in the right thoracic cavity or in the left thoracic cavity in some cases, and showed a distention of internal mammary veins and especially that of the pericardiacophrenic veins. No close relation was found between chylothorax and stomal findings. Histologically, no definite changes in pulmonary vessels supposed to cause the SVC hypertension were demonstrated.

5. Postoperative angiography—The contrast media injected into the superior vena cava smoothly entered into the right pulmonary artery (Fig. 4). But dogs with chylothorax or increased jugular venous pressure showed a marked distention of internal mammary veins and particularly the distention of the pericardiacophrenic veins.

Fig. 4.

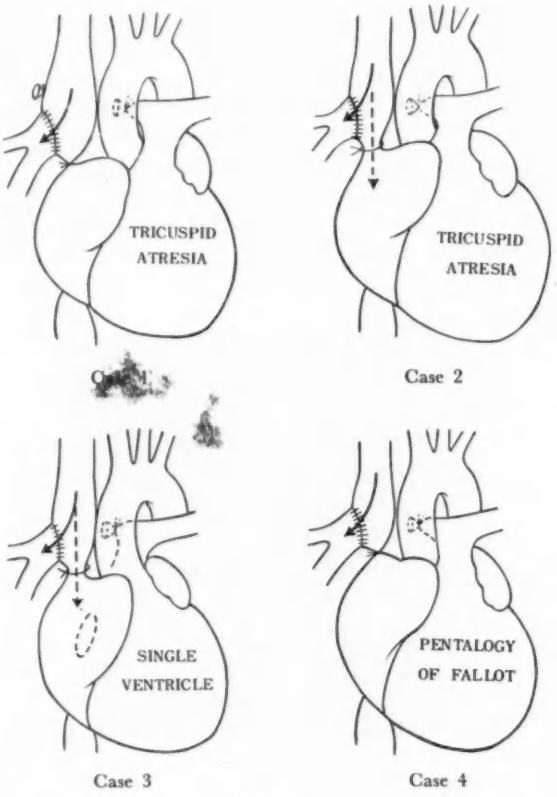
Clinical Experiences

Two cases with tricuspid atresia and one case with single ventricle and the pentalogy of Fallot were operated by SVC–RPA anastomosis.

Case 1. M. A.—A 10-year-old girl had severe cyanosis since birth and showed a progressive inability. Marked polycythemia and clubbing, left axis deviation of ECG, and the depressed pulmonary knob in the X-ray film were noted. The

catheter in the right atrium went into left side of the heart easily but not into the right ventricle. A diagnosis of tricuspid atresia was made from the clinical findings and the laboratory data.

On July 4, 1960, SVC-RPA side-to-end anastomosis was made and the proximal SVC was completely ligated. The lung biopsy before the anastomosis revealed no obstructive changes of pulmonary vessels. The pressure in the SVC rose to 400 mm.H_2O immediately after the operation with a hope that it would come down eventually (Fig. 5). Her cyanosis was improved and the peripheral



Case 2

Case 3

Case 4

Fig. 5.

arterial O_2 saturation rose from 76% preoperatively to 85% postoperatively, and she became able to tolerate more physical activities. The development of the chylothorax occurred a week after the operation as was expected from the experimental experience and she showed the so-called SVC obstruction syndrome. Frequent thoracocentesis, amounting several hundreds ml. each time was indicated and she received infusions of plasma for the correction of hypo-

proteinemia until the time of discharge 4 months after the operation. The cubital venous pressure was 250 mm. H_2O at the time of the discharge. The postoperative angiogram showed that the contrast media entered into the right pulmonary artery and into the markedly distended collateral veins simultaneously, suggesting the presence of the superior vena cava hypertension (Fig. 6).

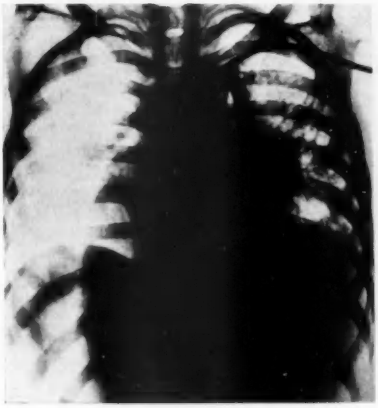


Fig. 6.

Case 2. F. T.—A 6-year-old boy with severe cyanosis and polycythemia since his birth had a slight systolic murmur at the 2nd and 3rd intercostal space of the left sternal border on physical examination. Pulmonary knob was depressed in the X-ray film. A tall P-wave and the left axis deviation was demonstrated in ECG. The catheter from right side of the heart went into the left heart easily but not into the right ventricle. He was diagnosed as having tricuspid atresia.

On Nov. 21, 1960, SVC-RPA side-to-end anastomosis was made. When the proximal SVC was constricted to one-fourth of its lumen after completion of anastomosis, pressure in SVC was 190 mm. H_2O. In this situation, when the proximal SVC was clamped, SVC pressure rose to 260 mm. H_2O, and when RPA was occluded, SVC pressure rose to 400 mm. H_2O. Because of these findings it was thought that the SVC blood entered more smoothly into RPA than into the right atrium and the constriction of the SVC was left out from any procedure (Fig. 5). Postoperatively, the cubital venous pressure fell to 120 mm. H_2O and of course there was no chylothorax. The cyanosis was markedly improved and the peripheral arterial O_2 saturation increased from 69% preoperatively to 87% postoperatively. The postoperative angiogram indicated an excellent anastomosis. Moreover, the contrast media did not enter into the right atrium (Fig. 7). He was discharged in an excellent condition 6 weeks after the operation.

Case 3. S. K.—A 6-year-old boy was severely cyanotic and frequently suffered from attacks of dyspnea. Systolic murmur, rather faint, was heard at the 3rd intercostal space of the left sternal border. An ECG showed a pattern of the right

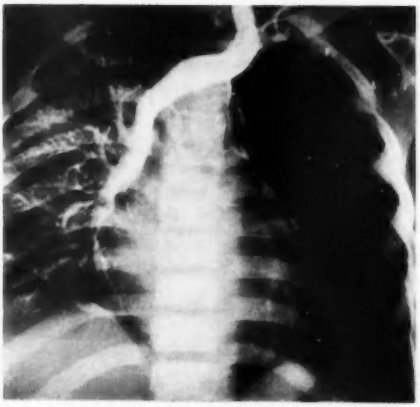


Fig. 7.

ventricular hypertrophy. The chest X-ray film revealed a very insignificant pulmonary knob, but the pulmonary vascular markings were not reduced.

He was operated on Dec. 21st, 1960, as the tetralogy of Fallot for the purpose of performing the Blalock-Taussig operation. But when the chest was opened at the left 4th intercostal space, it became obvious that he had a single ventricle with pulmonary stenosis. The pulmonary artery pressure was 20/7 mm. Hg. Extending the incision to the right thorax, side-to-end anastomosis was then attempted. After the completion of the anastomosis, the proximal SVC was constricted to about one-fourth of its lumen since the pressure in SVC was 215 mm. H_2O. Following these procedures the atrial septum was bored under the tactile manipulation through the right appendage expecting to obtain further improvement (Fig. 5).

Inspite of the bilateral thoracotomy, his respiration was well maintained by the Bird's respirator postoperatively. Unfortunately, however, he expired unexpectedly on the 3rd postoperative day due to anoxia caused by a hindrance of the respirator. On the postmortem examination, the operative diagnosis of single ventricle with pulmonary stenosis was confirmed. The anastomosis was completely patent and no chylothorax was found.

Case 4. Y. Y.—A 16-year-old boy was under-developed and severely cyanotic. A systolic murmur with slight thrill was demonstrated at the 2nd intercostal space of the left. ECG findings indicated neither the left axis deviation nor the ventricular hypertrophy. There was a free communication between the right side of the heart and the left ventricle in cardiac catheterization, but no right ventricular curve was obtainable. The chest X-ray film demonstrated the right atrial dilatation but neither the left nor the right ventricle showed any enlargement. The peripheral arterial O_2 saturation was 75.5%. The angiocardiography revealed that the contrast media was found to enter into the left atrium directly from the right atrium then to the left ventricle, the aorta and the pulmonary artery. Although the ECG findings were not typical of the tricuspid atresia, SVC-RPA side-to-end anastomosis was applied on Jan. 11, 1961.

Unexpectedly, the tactile examination through the right atrial appendage

revealed a large atrial septal defect, the normal tricuspid valve, and the pulmonary infundibular stenosis with the right ventricular hypertrophy. The pressure measurements showed that the aortic systolic pressure was equal to that of the right ventricle. An operative diagnosis of the pentalogy of Fallot was considered, and the same anastomosis was performed, since there was a dominant right-to-left shunt at the atrial level and the future corrective surgery was thought to be difficult. When the proximal SVC was clamped, the pressure in SVC rose from 135 mm.H_2O to only 180 mm.H_2O. The superior vena cava was completely ligated (Fig. 5). His postoperative course was uneventful, the peripheral arterial O_2 saturation increased from 75.5% to 83% and the cubital venous pressure was kept as low as 148 mm.H_2O.

Discussion

It has already been shown by Glenn et al. and Robicsek et al. that SVC-RPA anastomosis, that is, the partial right heart bypass was possible to be performed in dogs with the normal pulmonary vascular resistance. Since then successful applications of this method for tricuspid atresia,[4)5)] transposition of great vessels,[6)] Ebstein's disease[7)] and even the tetralogy of Fallot[8)] have recently been reported. Some practical and important problems for the clinical application, however, have not been well evaluated.

SVC–RPA anastomosis can be carried out by either the end-to-end type or the side-to-end type, but the superior vena cava must be completely occluded temporarily in the former type. Considering the fact that the brain may unavoidably suffer from the stagnant anoxia during the anastomosis particularly in the former group, the frequent occurrence of the early death in the former group seems to be related to, at least partially, the cerebral anoxia. SVC–RPA side-to-end anastomosis is, therefore, not only safer than the end-to-end anastomosis but has the advantage to be able to control SVC pressure easily by constricting the proximal superior vena cava.

This anastomosis is technically rather easy and a careful procedure will avoid the complication of both the thrombotic obstruction and the postoperative chylothorax. Postoperative chylothorax may be fatal for the experimental animal and is also very troublesome for the clinical case. Glenn et al. have showed the frequency of chylothorax to be about 60% in their dogs, but they did not correlate this complication with the pressure in SVC. In our experiments, however, a definite relation was found between SVC pressure more than 150 mm.H_2O and the occurrence of chylothorax.

Both the stomal factor and pulmonary (especially vascular) factor are related to the etiology of SVC hypertension after the operation, but no clear cut evidence of such was demonstrated in the present experimental studies. However, since the thrombotic obstructions in pulmonary arterioles

are sometimes found in cases with severe cyanosis and polycythemia, the pulmonary vascular factor can not be overlooked as the etiology of the postoperative SVC hypertension.

From the experimental results as well as the clinical data in the present study, it is quite obvious that the chylothorax is due to an elevated pressure in SVC. Santy[3] also reported a case of tricuspid atresia in whom the ligature at the proximal SVC had to be released because of the pressure in SVC over 400 mm.H_2O. The pressure in SVC must, therefore, be measured after the anastomosis and should be kept under 200 mm.H_2O by constricting the proximal SVC even though the effect of anastomosis may be somehow sacrificed.

It is very interesting to note that postoperative angiogram in some case (case 2) revealed the obstruction of the constricted proximal portion without any elevation of SVC pressure. Comparing this case with case 1, the pulmonary vascular factor seems to play an important role in the elevation of SVC pressure.

Finally, it may be concluded that this anastomosis may be indicated for the cyanotic lesions with reduced pulmonary flow and low pulmonary vascular resistance in some cases, but the malformation which can be anatomically corrected must be excluded from this indication, because this anastomosis is nothing but a sort of palliative procedures.

Summary

From the experimental results it was concluded that SVC–RPA side-to-end anastomosis was safer than end-to-end anastomosis, and that the proximal superior vena cava should be ligated or constricted in order to keep SVC pressure under 200 mm.H_2O since a definite correlation was found between the occurrence of postoperative chylothorax and an elevated SVC pressure.

Application of SVC–RPA side-to-end anastomosis to a total of 4 patients, including 2 patients with tricuspid atresia, one with single ventricle and another with pentalogy of Fallot, were made and excellent improvements were obtained in 3 cases. An early postoperative death was attributed to the mechanical failure of a respirator in one case.

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Inhibitory Effect of Sulfated Mono- and Polysaccharides on Experimental Hyperlipemia and Atherosclerosis in Rabbits

Katsumi MURATA, M. D.

Sodium salts of galactose disulfate and glucose monosulfate: both synthetically sulfated monosaccharides, starch sulfate: a synthetically sulfated polysaccharide, and calcium salt of carrageenin were given intravenously to cholesterol-fed rabbits. Inhibitory effects of these substances on the serum lipid patterns and atheromatous changes in the aorta were proved biochemically and histologically after their long term administration. Neither an anticoagulant activity in blood nor harmful effects were shown with the doses used. Further possible significance of the sulfated polysaccharides in the aortic tissue in relation with atherosclerosis and aging process was discussed.

THERE have been presented many reports that some of natural or synthetic sulfated polysaccharides including heparin inhibit lipemia and retard atherosclerosis, though there are differences in their extent.

Previously, the author[1] reported that sodium salts of sulfated polysaccharides obtained from seaweeds, namely carrageenin and laminarin sulfate, showed a remarkable antilipemic activity and also an inhibitory effect on the process of atherosclerosis induced in cholesterol-fed rabbits. Carrageenin,[2),3)] a natural sulfated polysaccharide, is composed largely of a chain of D-galactose residues linked through positions 1 and 3 and carrying a negatively charged sulfate group on position 4 and its molecular weight is reported to be between 9,000 and 120,000.[4)] Laminarin, seaweeds polysaccharide, is likewise a polymar of glucose and is easily sulfated and it has a relatively low molecular weight approximately 5,000.[5)]

In view of these conditions the experiments described here are mainly intended to ascertain the following points:

1. Whether even a low molecular synthetic sulfated monosaccharide such as galactose sulfate and glucose sulfate possesses the same inhibitory effects on lipemia and atherosclerosis induced experimentally.

2. Whether the calcium salt of carrageenin shows the same effects as well as the sodium salt.

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3. Whether the other synthetic sulfated polysaccharide has similar activities.

Materials and Methods

Sodium salts of galactose disulfate containing 16.2% sulfur and of glucose-6-monosulfate containing 11.3% sulfur were prepared for the first purpose. Calcium salt of carrageenin which was negative in a protein reaction, and sodium salt of starch sulfate which had 16.0% sulfur and a specific optical rotation of +89°, were also prepared for the second and third purposes.

The experiments were carried out as follows: the first experiment was undertaken during the course of 18 weeks for the first and second purposes and the second experiment was done for the period of 8 weeks for the third purpose. For the first experiment, 20 male albino rabbits which weighed about 2 Kg. at the beginning of the experiment, and 13 rabbits between 2.3 and 2.6 Kg. for the second experiment, were used. In order to induce hyperlipemia and atheromatous lesions, all the animals were fed daily about 250 Gm. of the bean-curd-mash containg cholesterol at the rate of 100 mg. per Kg. body weight throughout the course of the experiments. The animals of each experiment were randomly divided into test groups and their control groups.

The galactose sulfate-, glucose sulfate- (sodium salts), carrageenin (calcium salt)- treated groups and their control group which consisted of 5 rabbits respectively, were treated for the first experiment. The starch sulfate injected group of 6 rabbits and its control group of 7, were used in the second experiment. The animals of the test groups were individually given a daily intravenous injection of 5 mg. of each substance in physiological saline solution per Kg. of body weight, while the animals of the control groups received an equivalent injection of normal saline. Accordingly, the "control group" means the cholesterol-fed one along with physiological saline injection in these experiments.

For examining the lipid fractions in the various periods, the blood was drawn from the ear vein of the rabbits immediately prior to the experiments and at 2 week intervals during the entire course of the experiments. The measurements of serum lipid patterns such as total lipid, total and esterified cholesterol, phospholipid, β/α lipoprotein ratio and serum turbidity were done by the following methods.

Total lipid was determined by means of a turbidimetric method described by Huerga.[6]

Total and esterified cholesterol were determined by Sperry-Webb method[7] and its ratio was calculated.

Phospholipid was calculated from the value of phosphorus which was determined by Allen's method.[8]

β/α lipoprotein ratio. The lipoproteins were measured by paper electrophoresis by the method of Swahn.[9]

Turbidity. After the serum was diluted to 1 : 10 with distilled water, the turbidity of the dilute was measured in a photoelectric colorimeter using a 610 mμ. optical filter at a 10 mm. light path and expressed in value by 1,000 times of an optical density reading against a water blank.

At the end of the course of the experiments, all the rabbits were sacrificed in order to detect mainly atheromatous changes in the aorta and coronary arteries and any pathological changes in the other organs. After the aortic tube was removed and slit longitudinally, the visual grading of severity of the atheromatous lesions in the aorta was made into following 6 grades on the basis of the number and size of deposits or plaques to the entire length of the aorta.

0 presents no lesions.
1, minimum but definite and flat deposits.
2, more widely scattered flat deposits with a few pinhead-like or linear plaques.
3, lesions of several pinhead-like or linear plaques.
4, lesions of more widespread distribution with zonal or insular plaques.
5, severe deposits with a definite heaping of lesions with remarkable intraluminal protuberance.

The microscopic examination was carried out to ascertain the atheromatous lesions in the aorta. For this purpose, a number of specimens were taken from a part 5 to 10 mm. caudal from the origin of the left subclavian artery. The tissues were fixed in either 10% formalin or Zenker's solution, and then embedded in paraffin. Serial sections were stained with hematoxylin and eosin, periodic acid-Schiff's stain and Masson's trichrome stain combined with Gomori's aldehyde fuchsin stain. The frozen specimens were also cut serially and stained with Sudan III and 0.05% aqueous solution of toluidine blue. Microscopic observation was made, furthermore, in the other parts of the aorta, the coronary arteries, liver, kidney, spleen and adrenal gland.

Results

The results of biochemical analysis in the first experiment were summarized in Table I. As shown in Table I, calcium salt of carrageen was noticed to possess the most definite antilipemic activies, particularly in the mean levels of total lipid, total cholesterol and phospholipid, comparing with sodium salts of galactose sulfate and glucose sulfate, though all these sulfated monosaccharides showed an inhibitory action on serum lipids. In the carrageenin treated group, the inhibition of the rise of the mean level of total cholesterol was statistically significant in comparison to that of the control at the same period after 2 weeks following the beginning of the experiment. Significant differences in the mean levels of the total lipid and phospholipid were observed in this carrageenin group during nearly all the periods after 6 weeks from the start of this experiment. Even in the mean level of the total cholesterol and phospholipid ratio, significant differences were noted at 6 and 18 weeks. In the galactose sulfate- and glucose sulfate- treated groups, the inhibitory effect on the rise of serum lipids was generally shown in the latter half stage of the experiments. Significant differences in the mean levels of total lipid (glucose sulfate group only), total cholesterol, phospholipid, and cholesterol and phospholipid ratio, were obtained independently in each group of them

Table I. Serum Lipids in Galactose Sulfate-Injected, Glucose Sulfate-Injected, Carrageenin (Ca Salt)-Injected and Control Rabbits Fed Cholesterol

Duration (weeks)	Body weight (Kg.)	Turbidity	Total lipid (mg./100ml.)	Total cholesterol (mg./100ml.)	Ester ratio (%)	Phospholipid (mg./100 ml.)	C/P ratio
			Galactose sulfate				
Before	——	——	——	77 ± 8	64.1±5.7	109 ± 4	0.71 ±0.06
2	1.92±0.10‡	——	——	254 ±24	56.5±2.5	250 ±24	1.02 ±0.03
6	2.25±0.07	——	1105 ±223	205*±50	49.7±4.1	345 ±51	0.59†±0.06
8	2.22±0.06	——	1508 ± 50	307*±22	55.9±2.0	257*±21	1.20 ±0.05
10	2.30±0.07	——	1348 ±177	428 ±36	64.2±1.0	292 ±28	1.47 ±0.03
12	2.30±0.11	——	2028 ±310	429 ±65	58.7±4.1	257 ±32	1.67 ±0.20
14	2.37±0.09	13.2±2.7	1976 ±297	541 ±71	61.6±6.3	336 ±36	1.61 ±0.09
16	2.30±0.15	16.2±4.9	2140 ±428	423 ±98	68.2±3.6	359 ±81	1.18*±0.04
18	2.42±0.15	11.9±2.1	2180 ±171	337*±47	56.7±2.6	336 ±45	1.00*±0.05
			Glucose sulfate				
Before	2.13±0.05	——	——	80 ± 2	——	109 ± 3	0.73 ±0.03
2	1.97±0.07	——	——	272 ±18	67.5±5.8	260 ±28	1.05 ±0.01
6	2.12±0.14	——	970 ±177	234*±57	60.5±0.8	314 ±63	0.75*±0.08
8	2.23±0.15	——	1390*±120	297†±27	59.8±5.0	227†±16	1.31 ±0.07
10	2.24±0.10	——	1202*±153	351 ±46	59.5±1.7	253 ±32	1.39 ±0.07
12	2.10±0.07	——	1735 ±121	395 ±47	59.6±4.2	299 ±33	1.32 ±0.08
14	2.16±0.17	12.6±1.9	1794 ±109	610 ±52	66.2±1.4	372 ±25	1.64 ±0.09
16	2.21±0.23	8.0±0.8	2038†± 99	512 ±63	72.4±2.7	303 ±18	1.69 ±0.09
18	2.43±0.20	9.2±1.5	1847 ±127	229*±17	58.5±3.5	313 ±27	0.74*±0.04
			Carrageenin (Calcium salt)				
Before	2.19±0.09	——	——	79 ± 8	70.9±3.5	119 ± 7	0.66 ±0.04
2	——	——	——	149*± 9	55.0±2.4	204 ±21	0.73 ±0.06
6	2.31±0.06	——	673 ± 91	222†±27	59.4±2.1	258†±15	0.86*±0.02
8	2.34±0.11	——	590†± 20	298*±69	76.6±0.7	229*±47	1.30 ±0.04
10	2.37±0.08	——	1120 ±171	255*±72	65.0±1.9	233 ±44	1.09 ±0.06
12	2.30±0.11	——	1380 ± 56	283†±30	72.2±2.9	210*±33	1.35 ±0.10
14	2.34±0.06	6.0±0.6	810†±169	216†±47	71.8±2.6	177†±22	1.22 ±0.13
16	2.45±0.08	5.0±1.4	1138†± 72	243†±21	75.8±2.0	178†±18	1.37 ±0.07
18	2.49±0.08	6.0±0.9	748†± 45	118†± 6	56.3±1.9	151*± 6	0.78*±0.02
			Control				
Before	2.05±0.06	——	——	69 ± 8	67.7±6.7	103 ±15	0.67 ±0.03
2	2.00±0.04	——	——	294 ±30	66.7±3.1	256 ±44	1.15 ±0.01
6	2.31±0.05	——	1230± 96	402 ±20	60.0±4.9	382 ±20	1.05 ±0.05
8	2.33±0.09	——	1765± 53	554 ±18	64.9±4.6	398 ±39	1.39 ±0.09
10	2.42±0.05	——	1740±140	493 ±54	62.2±5.3	288 ±13	1.70 ±0.11
12	2.34±0.06	——	1545± 95	521 ±42	63.7±1.4	325 ±19	1.60 ±0.12
14	2.33±0.05	16.1±5.1	1648±136	603 ±35	68.8±2.7	331 ±26	1.83 ±0.05
16	2.39±0.07	12.3±2.7	2412± 58	593 ±71	75.2±1.2	380 ±30	1.56 ±0.17
18	2.63±0.05	13.7±3.4	2348±252	688 ±84	71.6±1.8	414 ±64	1.66 ±0.28

*.....$P < 0.05$

†.....$P < 0.01$

‡.....mean and standard error

Fig. 1. Atheromatous lesions in the thoracic aorta.
Left, cholesterol-fed and glucose sulfate treated rabbit (grade 1).
Right, cholesterol-fed control (grade 5).
Needle points intraluminal projection.

compared with those of control.

Macroscopic study revealed that the tendency of lesser atheromatous changes was generally seen in the treated groups, particularly in carrageenin treated group, in comparison to their control. The atheromatous lesions were frequently observed in the arch of the aorta and in the thoracic aorta where yellowish white plaques protuberated to form massive amorphous deposits. The elevated whitish small plaques were frequently noticed around the orifices of branches of the thoracic aorta and occasionally of the abdominal aorta. The ranges of the grading scale in the galactose sulfate-, glucose sulfate- and carrangeenin- treated groups were 0 to 4, 0 to 4 and 0 to 3 respectively and their averages in the grade were 2.85, 3.30 and 1.88 respectively. Contrariwise, that in the control group was 3 to 5, with an average of 3.84. Thus it may follow from these results that the visual findings confirmed the biochemical results revealing the suppressing effects of these sulfated mono- and polysaccharides on the hyperlipemia and atherosclerosis following cholesterol feeding.

Microscopic findings seem to be almost parallel to the gross observation as far as the atheromatous lesions in the aorta is concerned. In the initial stage, a foamy transformation was accompanied by mucinous metachromatic substances in the endothelium of the aorta (Fig. 2). In the more advanced stage, metachromatic and PAS postive substances appeared intensely just beneath the swollen layer of the intima. The intimal swelling developed gradually to form a cellular cushion causing the rupture of the elastica interna and lipid infiltration in this region (Figs. 3 and 4). In the severe case when a stratified proliferation of the intima (Fig. 5) proceeded towards the media, metachromasia underneath

Fig. 2. Changes in the intima of atheromatous lesions in the initial stage. The arrows show mucinous substances, which occur with increase in metachromasia, stain light green with Masson's trichrome. ei, elastica interna. Masson's trichrome stain combined with Gomori's aldehyde fuchsin stain, ×375.

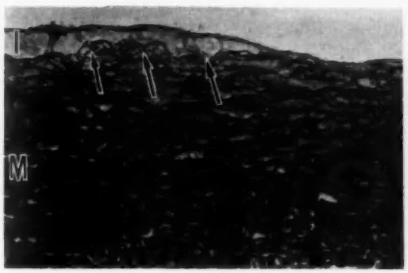


Fig. 3. The proliferated intima of a control rabbit. The arrows show the discontinuity and rupture of the elastica of the intima. Mucinous substances increase around the rupture. I, intima; M, media. Same stain as Fig. 2, ×93.

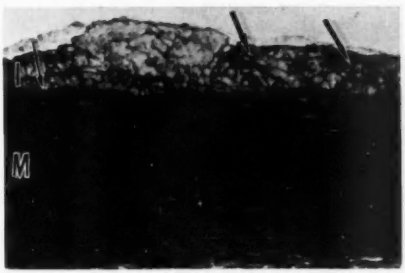


Fig. 4. The thickened and proliferated intima combined with foam cell formation of a control rabbit in the advanced stage. The accumulation of PAS positive substance in the atheroma is pointed by the arrows. Periodic acid-Schiff's stain, ×67.

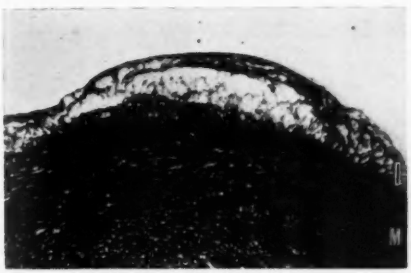


Fig. 5. Stratified proliferation of the intima of a control. Gomori's aldehyde fuchsin stain, ×38.

the intimal thickening usually faded away. Even in the treated groups, lipid droplet deposits were seen in the endothelium (Figs. 6 and 7), however, the lipid deposition was generally less than that of control rabbits. In the coronary vessels, atheromatous changes occurred occasionally in various sites, but the severity of coronary lesions could not be related to that of the aorta. Fig. 8 shows the intimal proliferation narrowing the lumen of the coronary artery with lipid deposits in the control rabbit.

Changes in the liver induced by cholesterol feeding were usually seen in the hepatic cells, in the Glisson's capsules and in the endothelial cells of

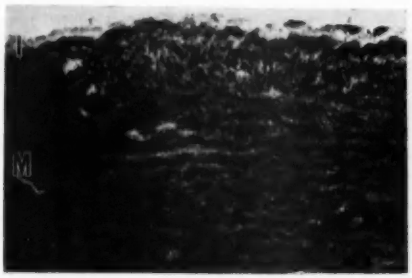


Fig. 6. Lipid droplets deposit in the intima of a galactose sulfate treated rabbit. Sudan III and hematoxylin stain, ×93.

Fig. 7. Lipid infiltration in the intima of a glucose sulfate treated rabbit. Same stain as Fig. 6, ×93.

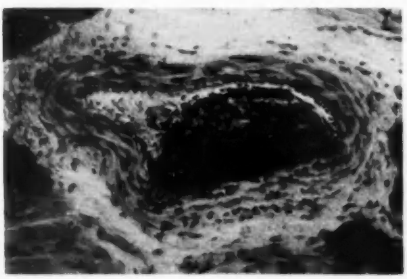


Fig. 8. The coronary artery of a control rabbit. Intimal proliferation with sudanophilic granules narrowing the lumen. Sudan III and hematoxylin stain, ×93.

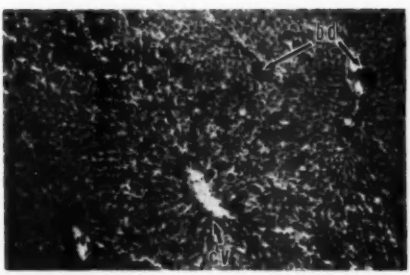


Fig. 9. The liver of a control rabbit. Note phagocyted fat droplets in the stella cells of Kupffer and in the bile ducts in Glisson's capsules. bd, bile duct; cv, central vein. Sudan III and hematoxylin stain, ×42.

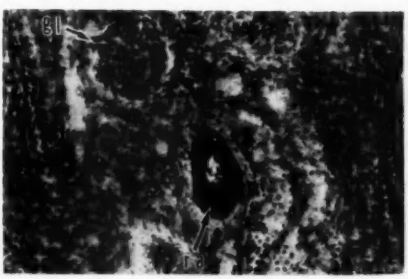
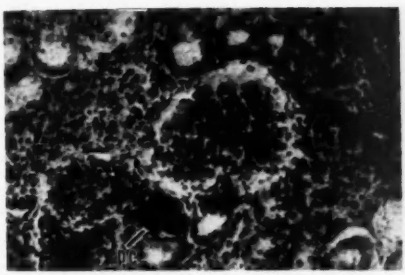
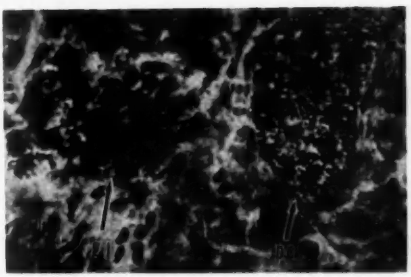


Fig. 10. Lipid deposition in the renal artery of a control rabbit. ra, renal artery. Sudan III and hematoxylin eosin ×140.

the sinusoidal capillaries. Enlargement of hepatic cell nuclei was occasionally observed in the early stage and vacuolization of the hepatic cells in the advanced stage. Phagocyted fat droplets were apparently found most frequently in the stella cells of Kupffer. It was difficult to recognize the differences of the damages in the liver between the treated and control groups. In the control animal, however, the bile ducts and hepatic arteries in Glisson's capsules were stained with Sudan III (Fig. 9). The kidney was rarely affected by cholesterol deposits. In gravely affected case in the control rabbits, however, lipid deposits were found in the wall of the





Figs. 11 and 12. Lipid deposition in the proximal convolution of a control rabbit. gl, glomerulus; pc, proximal convolution. Sudan III and hematoxylin stain. Fig. 11, ×190; Fig. 12, ×540.

Table II. Serum Lipids in Cholesterol-Fed plus Starch Sulfate-Injected Rabbits and in Cholesterol-Fed Rabbits (Control)

Duration (weeks)	Body weight (Kg.)	Turbidity	Total lipid (mg./100 ml.)	Total cholesterol (mg./100 ml.)	Ester ratio (%)	Phospholipid (mg./100 ml.)	C/P ratio	β/α lipoprotein ratio
				Starch sulfate				
Before	2.32±0.05‡	11.2 ±0.7	315 ± 21	55 ± 4	71.4±3.7	75 ± 5	0.74 ±0.01	1.99 ±0.12
2	2.39±0.12	12.0 ±0.7	590 ± 49	181 ±24	74.8±4.0	197 ±15	0.91 ±0.08	2.73 ±0.39
4	2.43±0.12	15.5*±1.4	679†± 83	176†± 5	65.3±5.0	202†±13	0.88 ±0.04	2.29†±0.12
6	2.40±0.10	10.5†±1.0	775*± 25	179†±32	65.2±1.3	155*± 5	1.15 ±0.17	1.99*±0.17
8	——	10.0 ±4.0	——	127*±35	70.9±0.6	144*±16	0.88†±0.03	2.31*±0.06
				Control				
Before	2.61±0.09	10.7±0.8	332± 47	58± 9	69.8±4.9	80±11	0.72±0.03	1.86±0.16
2	2.46±0.05	18.0±4.6	697± 78	196±28	78.7±2.1	263±42	0.75±0.04	2.97±0.16
4	2.61±0.07	31.1±1.7	1521±161	404±47	68.7±2.5	411±41	0.98±0.04	3.18±0.18
6	2.50±0.02	67.3±2.0	2150±234	591±45	63.3±2.7	410±42	1.44±0.05	3.29±0.28
8	2.53±0.09	77.8±9.5	2284±252	594±69	65.4±1.5	382±50	1.56±0.06	5.13±0.53

*.....$P < 0.05$
†.....$P < 0.01$
‡.....mean and standard error

renal arteries (Fig. 10). Figs. 11 and 12 also illustrate the lipid deposits in the proximal convolution of the control animal in Sudan III specimens.

The second experiment for the third purpose was carried out in the course of 8 weeks, using sodium salt of synthetic starch sulfate. The serum lipid patterns, as were illustrated in Table II, generally showed remarkable differences between the starch sulfate-injected group and its control after 4 weeks following the start of the experiment. The mean levels of total lipid and total cholesterol in the starch sulfate-treated group showed much less increase comparing with that in the control, with a statistical significance. The rising rates of the mean levels of phospholipid, and total cholesterol and phospholipid ratio in the treated group were significantly less in part than that in the control. In addition, the mean levels of β/α lipoprotein and serum turbidity of the treated group were also significantly lower in their increasing rate than that of control. It follows from this that starch sulfate has a suppressing effect on hyperlipemia induced in rabbits.

In the gross examination of the aorta, no atheromatous lesions were observed in all rabbits treated with starch sulfate, while a moderate grade of the atheromatous lesions, ranging from 0 to 2 with an average of 1.25 was demonstrated in the cholesterol-fed control rabbits. The atheromatous lesions in the control rabbits were mainly observed in the arch of the aorta, partly surrounding the orifices in the thoracic aorta.

Microscopic findings revealed the localization of these lesions in the intima. In the control rabbits, lipid infiltration was demonstrated in the intima with an increase in metachromatic, PAS positive substances in the subintima. In this instance, the accumulation of PAS positive substance was seen in the coronary artery without lipid deposition. In a few treated rabbits, lipid deposition was slightly noticed in the endothelium.

Fatty change in the liver was seen microscopically in the control and also in the other treated rabbits. There seemed to be no relationship between the degree of fatty change in the liver and the lipemia or atheromatosis.

Discussion

Besides the recent studies of sulfated polysaccharides in relation to aging process or atherosclerosis, sulfated polysaccharides has been intensely investigated since the discovery of heparin intending to obtain other heparin-like substances with an anticoagulant activity.

In 1936, Bergström[10] succeeded to obtain synthetically polysulfated monosaccharides, namely galactose tetrasulfate and glucose tetrasulfate containing 15.7% and 15.3% sulfur respectively. However, they failed to show anticoagulant activities, while starch trisulfate with 18.45% sulfur possessed a slight anticoagulant activity. Chargaff and his co-workers[11]

reported in 1936 in an investigation of inhibitory effects of high molecular substances on blood coagulation that galactan sulfate from seaweed containing 12% sulfur was found to be active in the inhibition of blood coagulant and sodium salt of cellulose disulfate was much more active than that of cellulose monosulfate. Subsequently, Astrup and his co-workers[12] noticed that starch sulfate, as well as cellulose and chitin polysulfate, had an anticoagulant activity. As pointed out by Fischer[13] and Bergström,[10] it was recognized already that the sulfate groups in sulfated polysaccharides might have an important role in their anticoagulant properties. Thereafter, Karrer and his co-workers[14] also stated that polysaccharides should be high molecular and sulfated for possessing anticoagulant properties. According to Ricketts,[15] dextran sulfate shows maximum activity in inhibiting blood coagulation when the number of sulfate groups exceeds an average of 1.3 per glucose unit. Recently, Donzelet[16] stated that dextran sulfate might be effective to inhibit development of arteriosclerosis, since this substance had a definite antilipemic activity.

On the other hand, it has been reported that not merely natural sulfated polysaccharides but also synthetic sulfated polysaccharides have a peculiar property showing metachromasia with basic stains.[17] The presence of sulfated mucopolysaccharides in the aorta has been assumed histochemically since the day of Virchow, as stated by Sslowjew in his report.[18] Metachromasia in the aorta, as has been noticed by Bunting,[19] is carried over from the fetal period throughout the life of individual and increases in its amount into the fourth decade after which it decreases accompanying loss of elasticity and increase of fibrosis. Moreover, metachromasia usually increases in the intima in the initial stage of atherosclerotic lesions, while it fades away with advancing of the aortic lesions, as mentioned previously in this report. Although not conclusive, it may be presumed from above observation that metachromasia in the aorta would have a certain relationship with changes in the aorta due to aging process or arteriosclerosis as related to the amount of sulfated polysaccharides.

Evidence is present concerning mucopolysaccharides in the aortic tissues that hyaluronic acid, chondroitin sulfate A and B, and heparitin sulfate have been isolated from the bovine and human abdominal aorta according to later reports by Meyer and his co-workers.[20] Dyrbye and Kirk[21] reported that the aortic mucopolysaccharide materials obtained from individuals of various ages decreased as a trend with age, but no significant change was observed in the sulfate values in the aorta with age.

In view of above observation, it should be reasonable to administer a suitable amount of sulfated saccharides for protecting aging process in the aortic tissues, even not presenting normally in the aorta. In these experiments not all substances have possessed any notable anticoagulant activities, even though their molecular sizes may differ considerably. Be-

sides carrageenin and starch sulfate showed clearly metachromasia *in vitro*, the other monosaccharides, galactose sulfate and glucose sulfate showed faint metachromasia *in vitro*. This could be due to their high sulfation. In these cases, it was rather difficult to have a definite trend of an anticoagulant activity as related to either an antilipemic activity or metachromasia and further to an inhibitory activity against atherosclerosis. However, as it was presumed that heparin and cellulose sulfate showed a much high anticoagulant activity due to their high sulfation,[11),22)] it seems to be likely that high sulfation of saccharides is necessary for possessing a high anticoagulant property in case of same structure and molecular weight, if disregarding the toxicity.

It is clearly seen from the experiments studied here that calcium salt of carrageenin possesses remarkable suppressing effects as well as sodium salt on lipemia and atherosclerosis, and synthetic starch sulfate has a same high property, moreover even the synthetic sulfated monosaccharides exhibit a tendency to inhibit hyperlipemia and cholesterol atherosclerosis. Accordingly, it would seem probable that the sufficient amount of sulfated saccharides in the arterial wall is required for maintaining a regular metabolism in the arterial tissues to avoid aging process and furthermore to repair arteriosclerotic changes.

Summary

(1) Synthetic galactose disulfate and glucose monosulfate exhibited a trend to inhibit hyperlipemia and atherosclerosis in cholesterol-fed rabbits by long term administration.

(2) Calcium salt of carrageenin showed experimentally similar inhibitory effects on atheromatous damages in rabbits due to hypercholesteremia, to sodium salt of carrageenin.

(3) Starch sulfate, a synthetic sulfated polysaccharide, decreased remarkably serum lipids and inhibited the development of atherosclerosis in cholesterol-fed rabbits.

(4) These sulfated saccharides failed to show their anticoagulant activities at least at the dosage used in these experiments.

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A Comparative Study of Four Lead Systems of Vectorcardiography

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Vectorcardiograms obtained by 4 different lead systems, Grishman's system, Wilson's system, Frank's system and Schmitt's system, were compared in normal subjects and cardiac patients.

The direction of the inscription of the QRS-loop, the direction of the half area vector and the maximal amplitude of X, Y and Z components of the loop were examined.

In normal subjects, similarity of the vectorcardiographic tracings by the 4 lead systems was satisfactory, that these 4 lead systems could be considered interchangeable. But this was not the case in cardiac patients, because dissimilar tracings were observed more frequently than in normal cases.

Both in normal and abnormal cases, very similar results were obtained by Frank's and Schmitt's lead systems.

Compared with Frank's or Schmitt's system, Z component in Grishman's system was smaller and Y component in Wilson's system was larger.

RECENTLY, several orthogonal lead systems of vectorcardiography have been devised and applied in practical use. On the other hand, the development of vectorcardiography has been hampered by a great number of different lead systems. It is, therefore, urgent to make an experimental and clinical comparison of different lead systems to find a correlation between the different lead systems.

There have been several reports[1)-10)] on a comparative study of various lead systems; orthogonal, cubic, and tetrahedron systems.

But, majority of these studies mainly concern with a comparison of corresponding lead vectors of these systems.

The purpose of this paper is to report the results of comparative study of 4 different lead systems, which are currently used for clinical purpose, in normal subjects and cardiac patients. This study was undertaken to determine the interchangeability of the results obtained by the 4 different lead systems.

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Material and Methods

The vectorcardiographic tracings were obtained in each subject by 4 different lead systems, viz., Cube system by Grishman and his associates,[1] Equilateral tetrahedron system by Wilson and his associates,[2] Orthogonal lead systems by Frank[13] and by Schmitt.[7]

Simultaneous photographic recordings of frontal, horizontal and sagittal projections were made with an instrument FVC-3 of Fukuda Medical Electrics Co. in Japan.

QRS-loops in each lead system were measured and following points were compared.

1. Direction of the inscription of the loop on each plane
2. Direction of half area vector[14]

   Half area vector was defined as a vector which should dissect the area of each QRS vector loop (Fig. 1). Mean vector could be approximated by half area vector[14] which were used as an index of spatial orientation of QRS-loop.

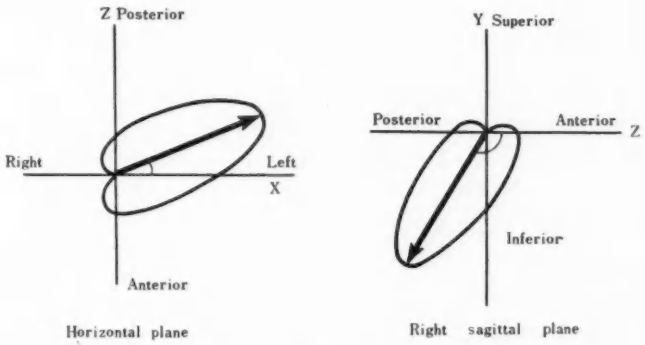


Fig. 1. Half area vector and its angular deviation.

Angles were measured from the leftward direction in the frontal and and horizontal planes and from the anterior direction in the sagittal plane.

3. Maximal amplitude of Y, X and Z components

   The X, Y and Z components of the QRS-loop were measured from 2 planes in each vectorcardiogram as shown in Fig. 2. The ratios of Y/X and of Z/X were calculated and compared with each different lead system in individual case.

The comparison of the ratios among different lead systems will not give the direct relationship of corresponding lead vectors, but it may help to indicate which axis is relatively exaggerated in the tracing obtained by that lead systems.

Among a total of 73 cases examined, there were 17 normal cases without any symptoms, signs, or history of cardiovascular disease and having normal electrocardiograms and chest X-rays, 36 cases with clinical and electrocardiographic

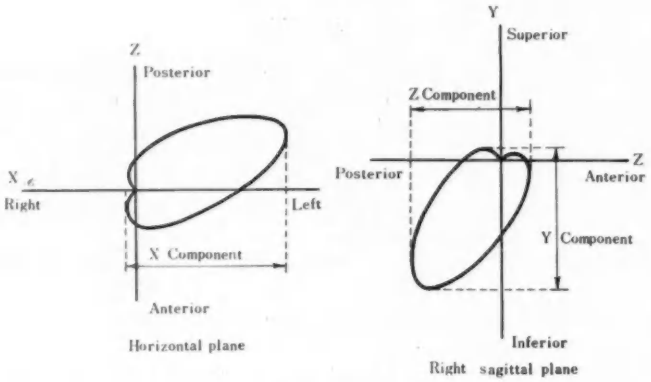


Fig. 2. Maximal amplitude of X, Y and Z components.

evidences of coronary sclerosis, and 20 cases with valvular diseases of the heart.

Results

1. Direction of the inscription of QRS-loop.

The direction is expressed as clockwise, counterclockwise or eight figured. Eight-figured contour was tentatively regarded as discrepant from either clockwise or counterclockwise inscription.

As the direction of the inscription of the loop is variable between leads even in normal subjects in the frontal plane, the discrepancies demonstrated in the sagittal and/or horizontal planes among the 4 lead systems were considered significant.

Table I. Comparison of the Direction of the Inscription of the QRS-loop in the Corresponding Plane on the Four Lead Systems

Group	Number of cases with the same direction on the four systems		Number of cases with disagreement of the direction		Total
	All planes	Horizontal and sagittal planes	Horizontal or sagittal plane	Horizontal and sagittal planes	
Normal	10	5	1	1	17
Coronary sclerosis	4	7	6	3	20
Valvular disease	19	6	8	3	36
Total	33	18	15	7	73

Results were shown in Table I.

The number of subjects in whom QRS-loops of each corresponding plane had the same direction in all 4 lead systems is; 10 cases among 17 normal subjects (59%), 19 of 36 with coronary sclerosis (53%) and 4 of 20 with valvular disease (20%).

With regard to the horizontal and sagittal planes, 15 of normal subjects (88%), 25 with coronary sclerosis (71%), and 9 with valvular disease (55%) showed the same direction on the 4 systems. Discrepancy of the inscription was frequently seen in cardiac patient.

The detailed description of 22 cases in which the direction of inscription disagreed in horizontal or sagittal plane in various lead systems is as follows:—In 11 cases disagreement was noticed only in horizontal plane, in 4 cases only in sagittal plane and in 7 cases both in horizontal and sagittal planes. Of all 22 cases, tracings obtained by Frank's system disagreed with that by Schmitt's system in horizontal or sagittal plane in only 8 cases including one normal case, 4 cases with coronary sclerosis and 3 cases with valvular disease.

When the leads of Frank and Schmitt were compared, 85% of all subjects had the same direction of the inscription of the loop in each corresponding plane.

In normal group, the direction of the inscription of QRS-loop in the horizontal and sagittal planes coincided in all cases except one, in whom the contour was eight-figured in both horizontal and sagittal planes in the Schmitt lead system.

2. The direction of half area vector of the QRS-loop.

Following methods were used to compare the half area vectors in each corresponding plane of the 4 systems.

In Fig. 3 an angle of the vector in Grishman lead was plotted against that in Wilson lead in individual cases. In Fig. 4 Frank lead and Schmitt lead were analysed in the same way.

A complete correlation should be indicated by these points on a straight line.

In Table II, calculated correlation coefficiency between measured values of angular direction of half area vector in each plane for every combination of 2 out of 4 systems is shown in 3 groups separately. (In Table II, (++) indicates p less than 1%, (+) less than 5%, (−) no correlation)

With regard to Frank and Schmitt lead systems, it was obvious from correlation coefficiencies higher than 0.9 in frontal and sagittal planes that the 2 systems were significantly correlated.

3. Comparison of maximal amplitude of X, Y and Z components.

Ratios of maximal amplitudes of Y and Z components to X component were calculated in each lead system.

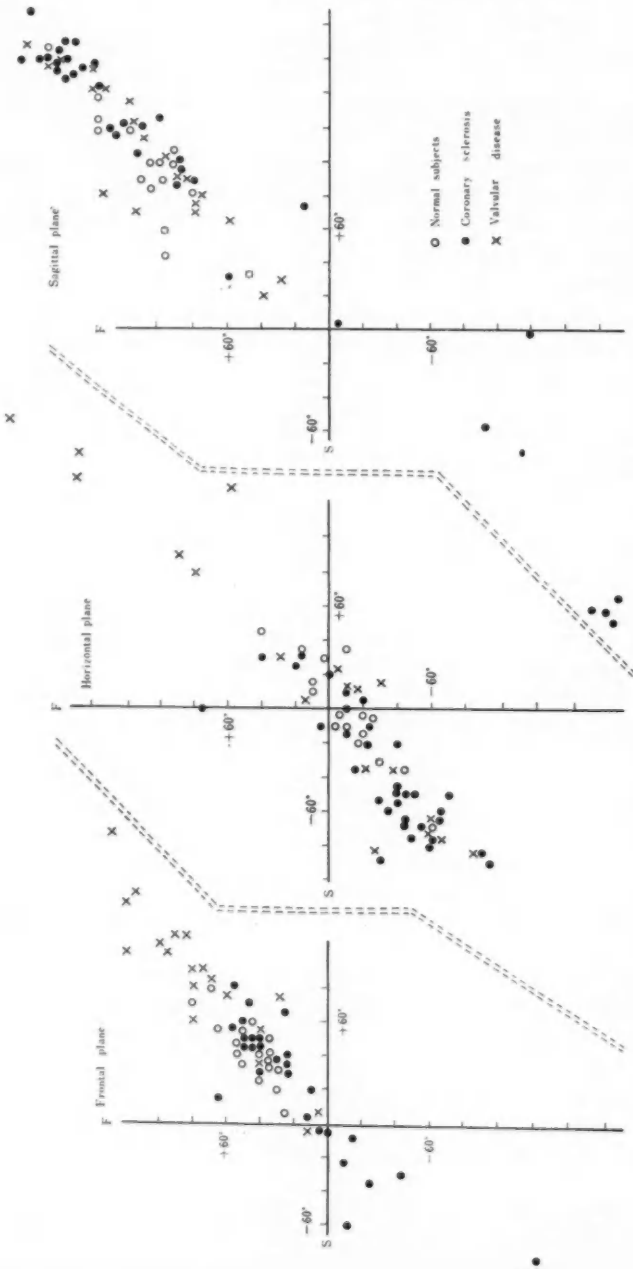
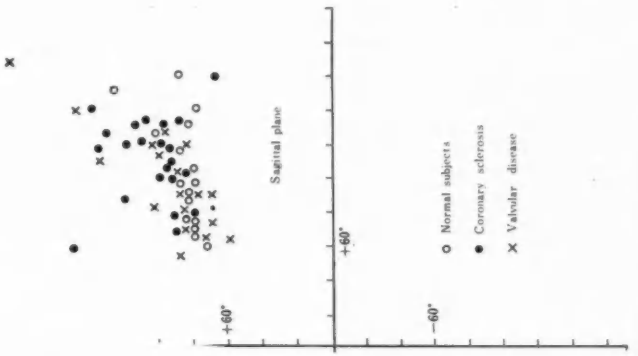


Fig. 3. Correlation of the direction of QRS half area vector between Grishman's system (G) and Wilson's system (W).



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The legend for Fig. 3 and that for Fig. 4 should be exchanged.

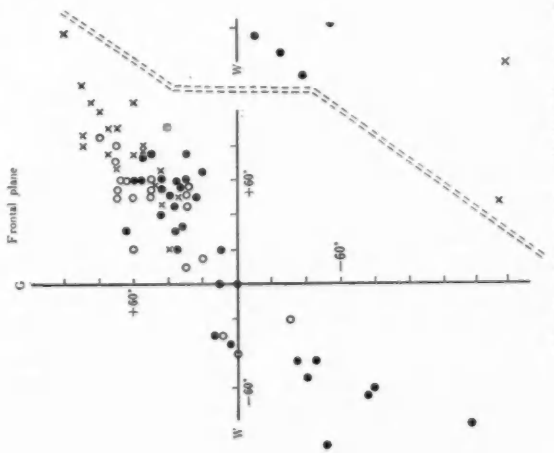

Fig. 4. Correlation of the direction of the QRS half area vector between Frank's system (F) and Schmitt's system (S).

Table II. Correlation Coefficiency of the Direction of the QRS Half Area Vector

Combination of the lead system	Frontal plane			Horizontal plane			Sagittal plane		
	Normal	Coronary sclerosis	Valvular disease	Normal	Coronary sclerosis	Valvular disease	Normal	Coronary sclerosis	Valvular disease
G—W	++(0.70)	+(0.57)	++(0.86)	++(0.71)	−(0.19)	++(0.78)	++(0.81)	++(0.91)	−(0.41)
G—F	++(0.75)	−(0.19)	++(0.88)	+(0.63)	−(0.10)	++(0.72)	++(0.83)	+(0.57)	−(0.11)
G—S	−(0.30)	−(0.10)	++(0.85)	+(0.61)	−(0.34)	++(0.70)	++(0.83)	+(0.53)	+(0.49)
W—F	+(0.66)	−(0.24)	++(0.87)	++(0.90)	++(0.76)	+(0.61)	++(0.83)	+(0.56)	++(0.80)
W—S	+(0.49)	−(0.24)	+(0.63)	++(0.80)	+(0.61)	++(0.74)	++(0.80)	+(0.46)	++(0.89)
F—S	++(0.92)	++(0.86)	++(0.93)	++(0.90)	++(0.76)	++(1.00)	++(0.91)	++(0.91)	++(0.91)

Note: G: Grishman's lead system, W: Wilson's lead system,
F: Frank's lead system, S: Schmitt's lead system

	++	+	−
r	<0.7		
p	$<1\%$	$<5\%$	−

Average values in normal subjects, patients with coronary sclerosis and those with valvular diseases were given in Table III.

Table III. Ratios of Maximal Amplitudes of Y and Z Components to X Component

		Grishman	Wilson	Frank	Schmitt
Normal	Y/X	1.9	2.0	1.2	1.1
	Z/X	0.5	1.0	1.0	1.2
Coronary sclerosis	Y/X	1.3	1.6	0.9	0.8
	Z/X	0.6	1.0	1.7	1.8
Valvular disease	Y/X	1.5	2.2	0.9	0.9
	Z/X	0.7	1.0	1.0	1.1

In Frank lead, the ratios were nearly the same with the corresponding values in Schmitt lead system in normal subjects and cardiac patients, therefore X, Y and Z components had similar magnitude in both lead systems.

Comparing with Frank lead system, Y/X ratio in Grishman system was larger, while Z/X ratio was smaller and Y/X in Wilson lead system was larger.

Discussion

Results of this study indicate that very similar tracings can be obtained by Frank and Schmitt lead systems. This is in agreement with Burger's result[2] and also with the transfer impedance analysis reported by Schmitt and his associates.[7]

In normal subjects, a slight deviation is noticeable in the direction of half area vector in the horizontal plane between Grishman lead and Schmitt lead, but, on the whole, a significant agreement in the direction of the half area vector and of the inscription of the loop in the 4 lead systems are indicated.

In patients with coronary sclerosis, disagreement of the direction of the inscription are noticed in some cases. Correlation of the direction of the half area vector is satistically not satisfactory in the horizontal plane between Grishman and Wilson lead, and also between Grishman and Frank lead systems.

In patients with valvular diseases, disagreement in the direction of the inscription is noticed more frequently than in other groups.

As for the differences between normal and abnormal conditions, Burger[2] stated that the difference in the contour of the QRS-loop is not significant, but mirror pattern study by Schmitt and his associates[15]-[17] indicated that applicability of a fixed dipole theory varied in several conditions. As a matter of fact, it is suggested by Langner and his associates that the disagreement between lead systems is more marked in cases with bundle branch block than in normal cases, while Sangiorgi[8] and Testoni[9] did not mention any remarkable difference in normal and abnormal conditions in their paper. In the present study, as far as the direction of the inscription and that of half area vector are concerned, these 4 lead systems are almost interchangeable in normal cases, but this is not the case in cardiac patients in whom discrepancies between these lead systems were observed more frequently.

Such a difference between vectorcardiograms obtained by various lead systems in subjects with heart diseases may be assumingly attributed to following factors:

1) The electrical field in abnormal condition deviates from that represented by a fixed single dipole.
2) Field is represented by a fixed single dipole, but the location of which is different from that in normal cases and exaggerated the difference of the corresponding lead vectors.
3) Changes in electrical properties of surrounding tissues iufluence the relation of lead systems used in this study.

Finally, the comparison of maximal amplitude of X, Y and Z components indicates that in normal subjects Z component is relatively small and Y component is large in Grishman lead system, and that Y component

is relatively large in Wilson lead. This fact is compatible with the results of Frank's study.[4]

Summary

(1) Vectorcardiographic tracings were taken by 4 different lead systems, viz., Cube system by Grishman, Equilateral tetrahedron system by Wilson, Orthogonal lead systems by Frank and by Schmitt in 17 normal subjects, 36 cases with coronary sclerosis and 20 cases with valvular heart disease.

The direction of the inscription of QRS-loop, the direction of the half area vector and the maximal amplitude of X, Y and Z components of the loop were examined.

(2) Very similar tracings can be obtained by Frank and Schmitt lead systems in most cases.

(3) In normal subjects, agreement of the 4 lead systems was satisfactory, but in patients with coronary sclerosis and valvular disease, these 4 lead systems could not be considered interchangeable.

(4) Compared with orthogonal system by Frank or Schmitt, Z component in Grishman's system is smaller and Y component in Wilson's system is larger.

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Special Article

Clinicopathological Study on the Thickening of Parietal Endocardium in the Adult Heart

Ryozo OKADA, M.D.

Careful examination of unselected 117 autopsied hearts revealed various degrees of pathological parietal endocardial thickening in 74% of them. A new classification of the pathological thickening of parietal endocardium is proposed. From the morphological standpoint, it is divided as (1) structureless fibrosis, (2) fibroelastosis, (3) thickening of the subendothelial layer, (4) thickening of all of the 5 layers (elastomyofibrosis), (5) thickening of the subendocardial layer, and (6) false thickening. From their pathogenesis, it is divided as (I) thrombogenic, (II) hypertrophic and/or hyperplastic, (III) exudative, edematous or deposited, and (IV) congenital. Endocardial fibrosis due to mechanical stimulation consists of the jet lesion which is divided as structureless scar and endocardial pocket, and the elastomyofibrosis. The endocardial fibroelastosis is concerned partly with cardiac dilatation. The endocardial change due to metabolic disturbance exhibits subendocardial edema or fibrosis (endocardosis).

SINCE Nagayo's study concerning the normal structure of parietal endocardium,[1),2)] a few systematic research on pathological endocardial thickening has been published.[3)-5),10)] Recently, the unusual form of heart disease with a marked endocardial fibrosis, for example, endocarditis parietalis fibroplastica (Löffler[6)]), endomyocardial fibrosis (Davies[7)]), diffuse endomyocardial sclerosis (Lynch and Watt[8)]), foetal endocardial fibroelastosis (Weinberg and Himelfarb[9)]) and so on, has drawn many attentions concerning the pathogenesis of this kind of disease. The present study was undertaken on the endocardial thickening with clear pathogenesis which encountered commonly at necropsy, in order to clarify the endocardial lesion with unknown pathogenesis. From the analysis of the materials, new classification of endocardial fibrosis based on morphology and pathogenesis was proposed and some clinicopathological consideration about miscellaneous form of endocardial lesions was made with the purpose of gaining a clue to find out some of the factors playing a role in the pathogenesis of unknown endocardial fibrosis.

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Material and Method

The hearts from 117 consecutive, unselected autopsied cases were carefully examined. All were from the Second Department of Internal Medicine, University of Tokyo, between 1958 and 1960. They consisted of 77 males and 40 females, whose ages ranged from 13 to 81 years, with an average of 47.8 years. The materials consisted of 42 cases of cardiac disease, 11 of chronic nephritis, 17 of liver cirrhosis, 22 of malignant tumor, 9 of pulmonary disease, 6 of blood disease and 10 of others. The hearts were weighed after removal of the extracardiac tissue and the aorta above the aortic valve. The thickness of the valve leaflets were measured by micrometer. The degree of atherosclerosis of aorta and coronary arteries was described according to Gore's grading,[11] and atherosclerosis index was calculated. The volume of each chambers of the heart was estimated by ballooning method* after its fixation in Formalin. The grade of parietal endocardial thickening was macroscopically classified as: none (−), slightly opaque (+), moderately white with not elevated surface (++), markedly white with elevated surface (+++), and extremely thickened scar formation (++++). The distribution of these changes was described geographically in the cardiac map[12] which had I to XIV divisions as longitude, and 1 to 3 divisions for both ventricles and 1′ to 2′ divisions for both atria as latitude, showing geographically developed endocardial surface by Goode's method (Fig. 1). Tissue slices were taken from interventricular

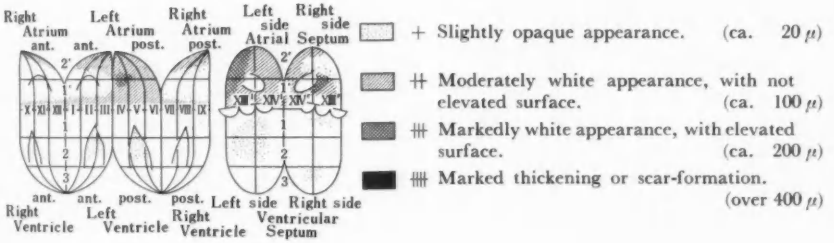


Fig. 1.

septum with holizontal cut at 2 cm. beneath the semilunar valves, including endocardium of the outflow tract of both ventricles, from anterior and posterior wall of both ventricles with vertical cut including papillary muscles, from posterior wall of both atria, as well as from areas with abnormal endocardial thickening. The tissue specimen was fixed in Formalin, and was embedded mostly in paraffin or partly in carbowax, and the sections were prepared in the usual manner. They were stained with hematoxylin-eosin, Mallory's azan or Masson's trichrome, and Weigert-van Gieson's technique for elastica, smooth muscle and collagen. PAS and Sudan III stain were also applied whenever it was needed.

* A method for volume estimation of the heart. Water is injected into a balloon which fulfils arbitrary cavity of the heart. The volume of the water indicates the volume of lumen of the heart.

Results

(1) Normal parietal endocardium: From 27 cases with macroscopically normal endocardium without cardiac, pulmonary, hypertensive, anemic and hepatic disease, it was proved that physiological thickening of endocardium was observed at the outflow tract and papillary muscles of the left ventricle, the outflow tract and apical portion of the right ventricle and the anterior portion of atrial septum as well as posterior wall of both atria (Fig. 1). These findings have prompted the author to designate this geographical distribution of endocardial thickening as "normal or physiological pattern."

In microscopic examination of the normal endocardium, it became apparent that the thickness of mural endocardium became thicker with age and grossly paralleled the thickness of aortic valvular leaflet (Fig. 2). The

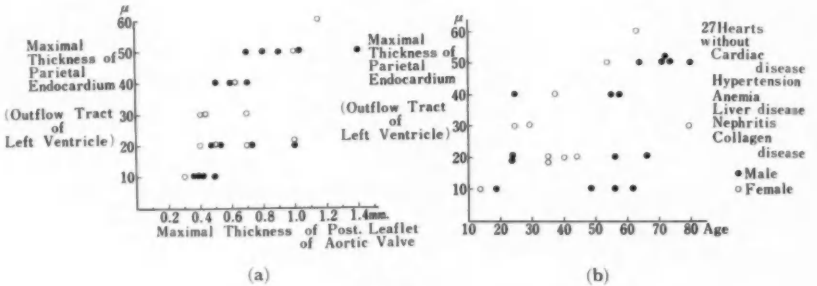


Fig. 2.
(a) Correlation between thickness of parietal endocardium and aortic valvular leaflet.
(b) Age and thickness of parietal endocardium.

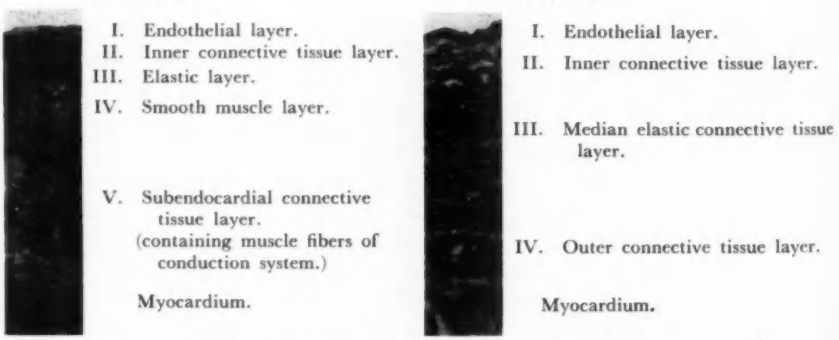


Fig. 3. Normal structure of parietal endocardium.

normal structure of parietal endocardium has been described in detail by Nagayo.[1] He divided it into 5 layers at the left ventricle and into 4 layers at the both atria (Fig. 3). Fig. 4 shows the thickness of endocardium and that of its individual layer measured microscopically in above mentioned cases. The mean thickness of the normal endocardium was 20 μ at the outflow tract and papillary muscles of the left ventricle, 10 μ at the antero-posterior wall of the left ventricle and the outflow tract and papillary muscles of the right ventricle, 7 to 8 μ at the antero-posterior wall of the right ventricle, 300 μ at the posterior wall of the left atrium and 100 μ at the posterior wall of the right atrium (Fig. 4). The author designated

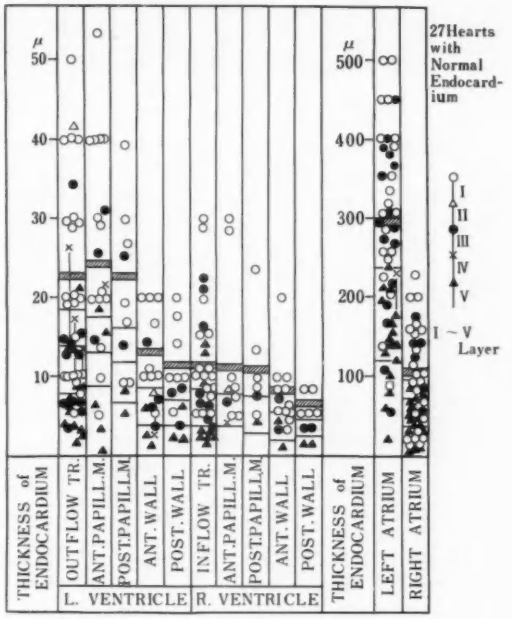


Fig. 4. Physiological distribution of parietal endocardial thickness.

the endocardium which had these 5 or 4 layers and normal thickness, as "normal histological type" of the endocardium.

(2) Jet lesion: So called jet lesion appeared at the parietal endocardium where the jet stream of blood struck, as a result of abnormal intracardiac hemodynamics.

(a) Impact zone of the jet stream with vertical direction: Fig. 5 shows the endocardial scar of 2.2×6 cm. in size and 2 mm. in thickness, at the lateral wall of right ventricle where the jet stream struck with almost vertical direction to the wall through 0.7×0.7 cm. sized interventricular

(a) (b)

Fig. 5. Jet lesion.

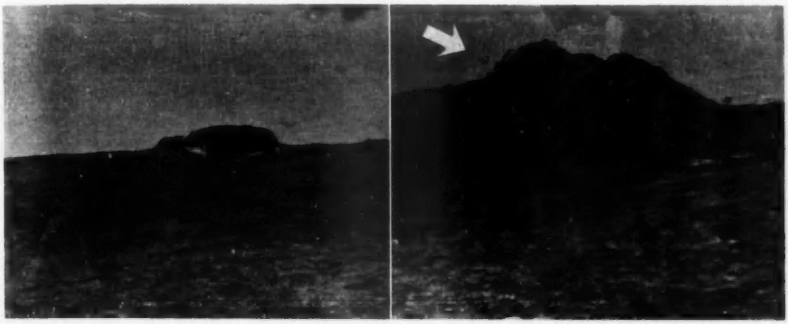
(a) Endocardial scar in the right ventricle due to jet stream from the ventricular septal defect (arrow mark shows source of jet stream).

(b) Microscopical view of structureless endocardial fibrosis with overlaid thrombus. A few capillary invasion but without elastic proliferation.

Azan stain. 40×

septal defect. Histological research of the lesion disclosed a homogenous and structureless fibrosis with red thrombus on its surface. This fibrosis was lost the primary structure of endocardium completely and had a few invasion of capillaries, but neither cellular infiltration nor elastic fiber.

(b) Impact zone of the jet stream with oblique direction: Many cases of valvular disease of the heart had jet streams with oblique direction to the parietal endocardium. For example, the jet stream of aortic regurgitation struck the outflow tract of left ventricle, that of aortic stenosis struck the wall of aorta, that of mitral insufficiency struck the posterior wall or vertex of left atrium, that of mitral stenosis struck somewhere in the left ventricle and that of pulmonary valvular lesions struck the pulmonary artery or the right ventricle. In some of these cases, such as aortic regurgitation and mitral insufficiency, the area of endocardium struck by the jet stream showed fibrotic thickening which had a sickle form and directed with its concavity and sharp limitation towards the source of the jet stream (Fig. 6 (b)). This fibrosis developed a pocket-form fibrosis opening towards the source of the jet stream, and finally a endocardial pocket[13] or pseudovalve of 0.3 to 2 cm. in size. Sometimes, multiple pockets were observed (Fig. 7 (a)). In histological examination, the pocket had neither vascularity nor inflammatory sign, and it consisted of looser connective tissue near the surface and denser collagen fibers at the basis in the relatively fresh pocket. In the considerably old pocket, elastic fibers were arranged only near the surface, and took fan-shaped arrangement from



(a) (b)

Fig. 6. Jet lesion. (PAS Stain. 100x)

(a) Initial stage of jet lesion. Fibrinthrombus deposits on the apparently normal endocardium of left atrium.

(b) The organizing fibrin thrombus has sharp limitation towards the source of jet stream (arrow mark).

(a) (b)

Fig. 7. Endocardial pocket.

(a) Aortic regurgitation. Multiple endocardial pockets on the outflow tract of left ventricle.

(b) Frontal cut-surface of endocardial pocket. Almost normal elastic layer and subendocardial connective tissue layer.

Elastica van Gieson's stain. 40×

both edges of the cusp. All of the pockets maintained characteristically the primary structure of endocardium beneath almost undamaged elastic layer at the basis (Fig. 7 (b)). Therefore, this type of fibrosis consisted of thickened subendothelial (inner) connective tissue layer. The other cases with relatively weak jet streams had the jet lesions which consisted of

simple subendothelial fibrosis. These lesions showed a localized or patchy thickening of the inner connective tissue layer and had almost normal endocardial structure beneath the elastic layer. The endocardial pockets or subendothelial fibrosis exhibited almost the same feature in both rheumatic and luetic heart diseases.

The incidence of jet lesion is demonstrated in Table I. Among 39

Table I. Incidence of Jet Lesion and Endocardial Pocket

Case	Number of cases	Jet lesion	Probable jet lesion	Incidence	Endocardial pocket
Aortic insufficiency	15	13	2	100%	4
Aortic stenosis and insufficiency	1	1	0	100	0
Aortic stenosis	1	0	1	100	0
Mitral insufficiency	4	2	1	75	2
Mitral stenosis and insufficiency	10	5	3	80	1
Mitral stenosis	2	0	2	100	0
Tricuspid insufficiency	3	2	0	67	0
Pulmonary insufficiency	1	0	1	100	0
Atrial septal defect	1	0	0	0	0
Ventricular septal defect	1	1	0	100	0
Total	39	24	10	87%	7

hearts with valvular deformity or abnormal shunt, 87% of total cases and 100% of aortic valvular lesion had jet lesion. In the table, probable jet lesion indicates the fibrosis which may be assumed as the result of jet lesion but the possibility of endocarditis causing this lesion can not be completely ruled out.

(3) Friction zone (Elastomyofibrosis): Macroscopically, whitish thickened endocardium of the outflow tract of the left ventricle appeared in 75% of the heart with persistent hypertension (Fig. 8 (a)). This appeared most markedly at the endocardium on the shoulder of hypertrophied interventricular septum convexed towards the left ventricle. Histological finding of this lesion showed marked hypertrophy and hyperplasia of all of the 5 layers of endocardium (exaggerated normal histological type), especially of the smooth muscle layer (Elastomyofibrosis,[5] Fig. 8 (b)). The geographical distribution of this type of endocardial thickening maintained physiological pattern. The most remarkable thickening of the friction zone was measured up to 300 μ in thickness at the outflow tract and papillary muscles of the left ventricle.

There was apparently significant correlation between the thickness of the smooth muscle layer at the outflow tract of the left ventricle and the maximal blood pressure. Especially close correlation was proved in the hypertensive group with blood pressure of more than 160/100 mm.Hg (Fig. 9).

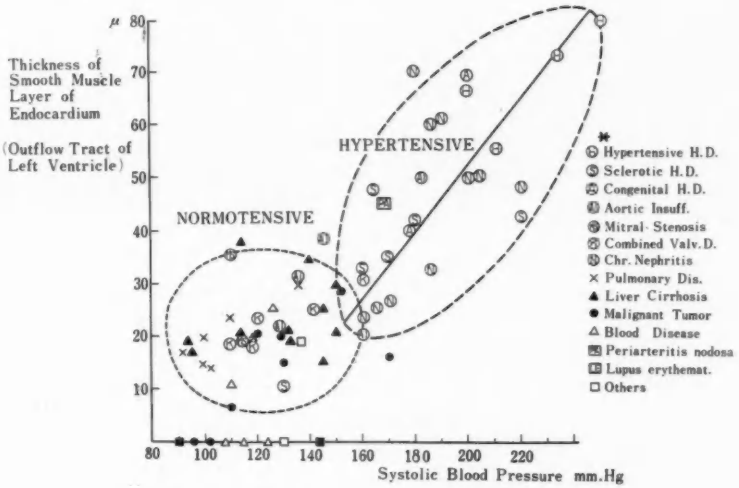
(a) (b)

Fig. 8.

(a) Hypertensive heart disease. Whitish thickening of endocardium at the outflow tract of left ventricle.

(b) Elastomyofibrosis of endocardium. Hypertrophied and hyperplastic smooth muscle layer.

Elastica van Gieson's stain. 100×



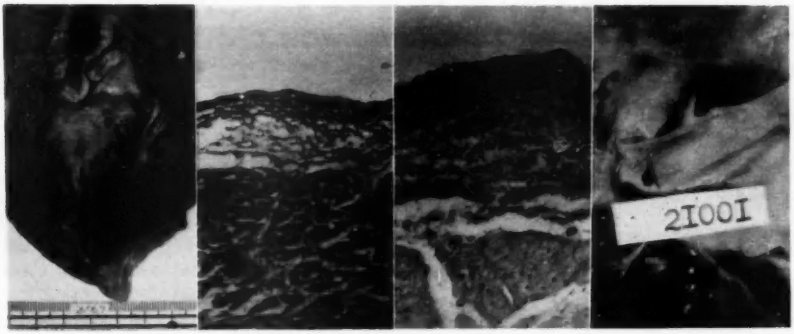
* These symbols are common in the following figures.

Fig. 9. Thickness of smooth muscle layer of endocardium and blood pressure.

If the thickness more than 30 μ of the smooth muscle layer was assumed as pathological, 75% of hypertensive group (21/28), 13% of aortic regurgi-

tation (2/16) and 7% of normotensive group (6/73) had the pathological elastomyofibrosis. Especially the heart of the chronic glomerulonephritis with terminal uremia showed a tendency of macroscopically diffuse, whitish and edematous appearance of endocardium. It exhibited elastomyofibrosis complicated with subendocardial edema (endocardosis) in histological finding. The degree of elastomyofibrosis was also related with the grade of hypertrophy of muscle fibers in myocardium. No abnormal finding was discovered in this lesion by PAS or Sudan III stain.

(4) Endokardose or endocardosis: In the case with the persistent general metabolic disturbance, such as liver cirrhosis and uremia, one could frequently discover myocardial degeneration which has been mentioned as Wuhrmann's Myokardose.[14] The parietal endocardium in such a case with metabolic disturbance characteristically showed a marked edema or invasion of a certain plasma component in the subendocardial space. The highest grade of subendocardial edema was seen in the subacute yellow liver atrophy and uremia (Fig. 10 (b)), and successively increased collagen fibers



(a) (b) (c) (d)

Fig. 10. Endocardosis.

(a) Liver cirrhosis. Macroscopical view of endocardium of left ventricle.
(b) Liver cirrhosis. Subendocardial edema.
Elastica van Gieson's stain. 100×
(c) Liver cirrhosis. Subendocardial fibrosis.
Elastica van Gieson's stain. 100×
(d) Liver cirrhosis. Marginal villi on the aortic valvular leaflets (A special type of Lambl's excrescence).

in the subendocardium were observed in the long standing portal liver cirrhosis (Fig. 10 (a), (c)). The grade of subendocardial edema or fibrosis was fairly well correlated with the lowering of serum albumin level (Fig. 11). The almost same change was observed in the endocardium of both atria in the case with metabolic disturbance, however, in such a case the edematous process was observed not only in subendocardial layer, but even

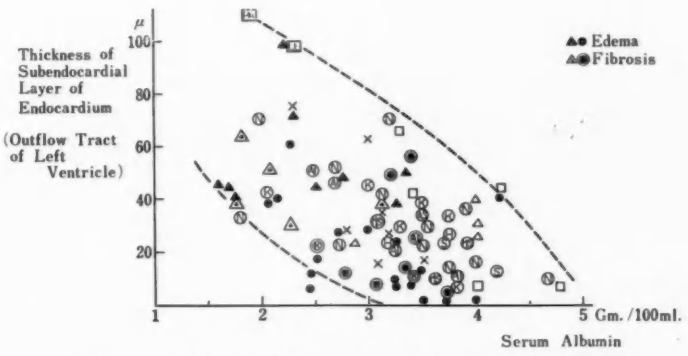


Fig. 11. Thickness of subendocardial layer and serum albumin (Endocardosis).

in the inner and median layer of the endocardium itself. PAS and Sudan III stain could reveal no specific abnormality.

The subendocardial edema or fibrosis was frequently accompanied by marginal villiform processus (Lambl's excrescence) on the noduli arantii of aortic valvular cusps which consisted of deposited or organized fibrin-like substance (Fig. 10 (d)). This type of endocardial changes should be called as "Endokardose or endocardosis".[15] The geographical distribution of this endocardial change had a certain tendency to be preponderant at the inflow tract of the both ventricle, which was contrary to the normal distribution (Table VI (a)). The incidence of endocardosis was demonstrated in Table II, and was high in liver cirrhosis and uremia.

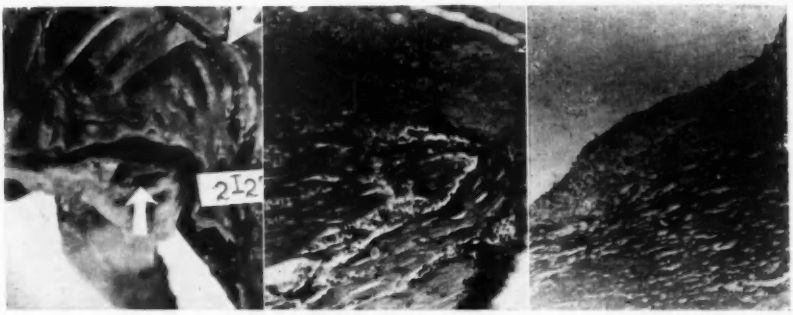
Table II. Endocardosis

Case	Number of cases	Endocardosis	Incidence
Liver cirrhosis	17	16	94%
Chronic nephritis	11	8	73
Pulmonary disease	9	7*	78
Blood disease	6	4	67
Malignant tumor	22	6	27
Cardiac disease	42	7	17
Collagen disease	2	(2)**	(100)
Others	8	1	12
Total	117	51	43%

* Only at right ventricle
** With inflammatory reaction

(5) Endocardial fibrosis resulted from reparative process: Destructed parietal endocardium in myocardial infarction was covered immediately

with thrombus. An organization of the overlaid thrombus was followed by endocardial fibrosis (Fig. 12 (a), (b)). If the overlaid thrombus was



(a) (b) (c)

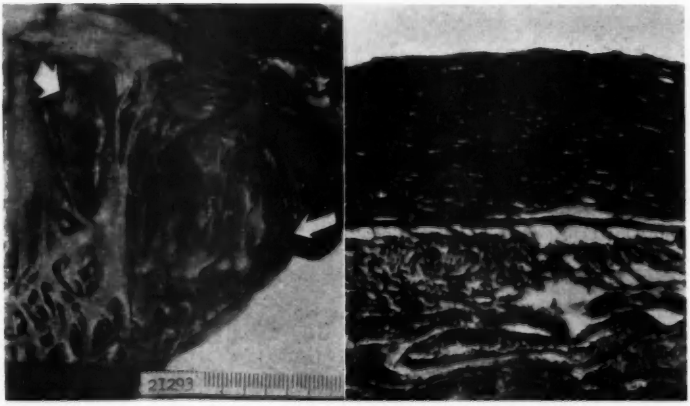
Fig. 12. Reparative fibrosis.

(a) Fresh myocardial infarction. 14 days after the last attack.

(b) Destruction of endocardium due to myocardial infarction. 1 day after the attack. Elastica van Gieson's stain. 400×

(c) Creeping fibrous tissue on the fibrin thrombus. Elastica van Gieson's stain. 100×

too large, a creeping overgrowth of new connective tissue along the surface of thrombus was observed (Fig. 12 (c)). This type of endocardial fibrosis had homogenous proliferation of collagen fiber and had, of course, no primary endocardial structure. An older endocardial scar had few capillaries and no cellular infiltration. In a relatively fresh endocardial



(a) (b)

Fig. 13. Endocardial fibroelastosis.

(a) Old myocardial infarction (arrow mark).

(b) Endocardial fibroelastosis. Elastica van Gieson's stain. 100×

fibrosis of this type, no increase in elastic fiber was found. On the contrary, in the endocardial fibrosis whose process persisted more than 6 months after the attack of myocardial infarction and was influenced by some distension due to aneurysmal change of the ventricular wall, the proliferation of elastic fibers became marked. In such a case, the elastic fibers were arranged regularly and oriented parallel to the lumen, and the homogenous fibroelastosis was completed (Fig. 13 and Fig. 14 (b)). No endocardial fibro-

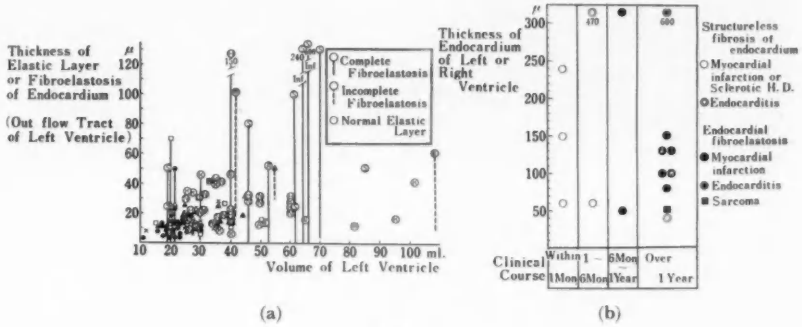


Fig. 14.

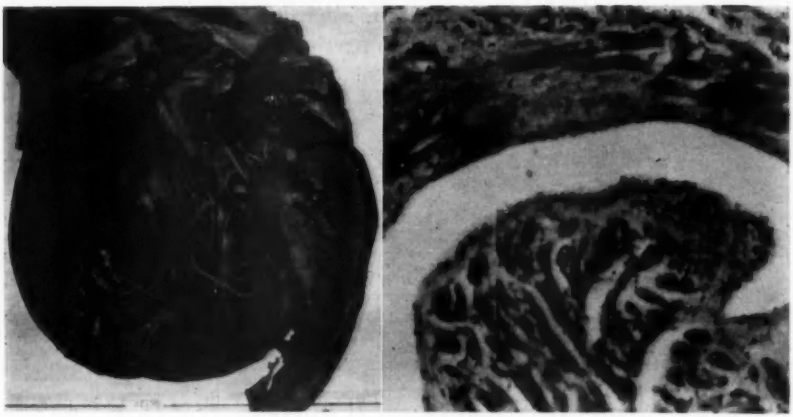
(a) Thickness of elastic layer or fibroelastosis of endocardium and cardiac dilatation.

(b) Time-factor in the pathogenesis of endocardial fibroelastosis.

elastosis was observed without previous destruction of the endocardium.

The graphical demonstration of the relationship between the thickness of the elastic layer or fibroelastosis of the parietal endocardium and the left ventricular volume (Fig. 14 (a)), indicates that no marked increase in elastic fiber was seen in the endocardium with normal structure, though a considerable dilatation of the ventricle was present, but that the fibroelastosis became marked and grossly paralleled the dilatation of the ventricle in the previously destructed endocardium.

(6) Endocardial fibrosis due to parietal endocarditis: The most popular parietal endocarditis having some possibility to develope endocardial fibrosis was of rheumatic origin. The initial histologic picture was focal monocytic infiltration or appearance of Ashoff's nodule in the swollen endocardium (Fig. 15). A chance to catch the early stage of this change was so rare, as seen in the present study, that only one case of such was found among 14 cases of rheumatic heart disease. Localized proliferation of the subendothelial connective tissue (Fig. 16) (6/14), the subendocardial fibrosis (5/14), the structureless fibrosis (3/14) and the fibrinoid degeneration or necrosis of the endocardium (3/14) were frequently observed in rheumatic heart disease (Table III). A case with structureless endocardial fibrosis



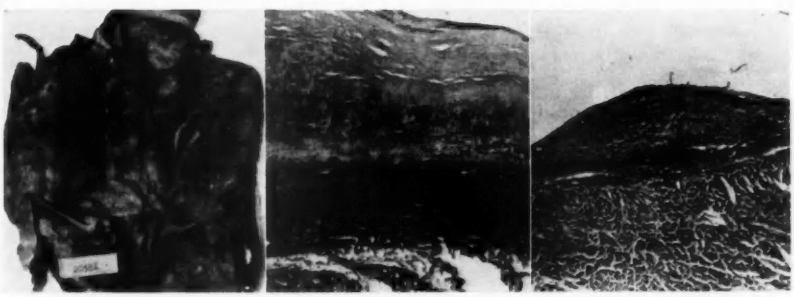
(a) (b)

Fig. 15. Rheumatic endocarditis.

(a) Combined valvular disease. Irregular patchy endocardial thickening of the left ventricle.

(b) Fresh rheumatic parietal endocarditis.

H. E. stain. 400×



(a) (a) (c)

Fig. 16. Rhumatic endocarditis.

(a) Mitral stenosis. Diffuse irregular endocardial thickening of the left atrium.

(b) Markedly thickened subendothelial layer with capillary invasion and mononuclear cell infiltration in the deeper layer.

Elastica van Gieson's stain. 40×

(c) Focal thickening of the subendothelial layer with sparse remnant of the normal structure of endocardium.

Elastica van Gieson's stain. 100×

that showed a characteristic feature of rheumatic change is demonstrated (Fig. 17 (a)). The endocardium of such a case consisted of a dense

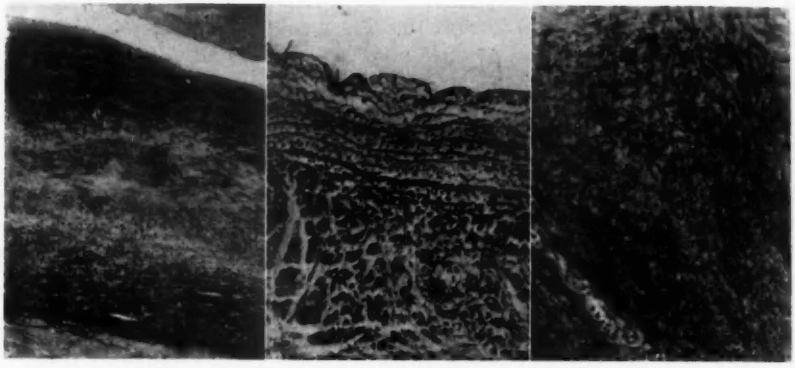
Table III. Parietal Endocardial Thickening due to Endocarditis

Histologic finding \ Endocarditis			Acute bacterial	Subacute bacterial	Rheumatic	Luetic	Unknown
Localized abscess formation			1	—	—	—	—
Diffuse subendothelial hyperplasia			—	2	—	—	1
Localized subendothelial hyperplasia			—	—	6	4	1
Focal cellular infiltration or granuloma			—	—	1	—	—
Fibrinoid degeneration or necrosis			—	—	3	—	—
Cellular infiltration in median layer			—	—	1	—	—
Subendocardial fibrosis			—	—	5	2	1
Fibrosis lost primary structure			—	—	3	1	1
Distribution of lesions	Left ventricle	Outflow tract	—	2	8	2	2
		Inflow tract	1	1	5	1	—
	Right ventricle	Outflow tract	1	1	3	—	—
		Inflow tract		—	—	—	—
	Left atrium	Anterior wall	—	1	7	—	—
		Posterior wall	—	1	12	—	—
	Right atrium	Anterior wall	—	—	2	—	—
		Posterior wall	—	—		—	—
Total			1	2	14	5	2

avascular scar with irregularly arranged delicate elastic fibers in the superficial layer and increased capillaries with infiltration of monocytes and hemosiderin-laden histiocytes in the deeper layer (Fig. 17 (a)). This complicated lesion might exhibit a chronic and recurrent nature of rheumatic endocarditis. Above mentioned miscellaneous and complicated types of the endocardial fibrosis of rheumatic origin were commonly seen as localized or patchy fibrosis at the posterior wall of left atrium (Fig. 16) or in the left ventricle (Table III).

In the luetic heart disease, subendothelial fibrosis of the endocardium was frequently observed at the outflow tract of the left ventricle, but it was very difficult to differentiate this change from the jet lesion since the aortic regurgitation was most frequently found in the luetic valvular disease. In 4 cases of such, the endocardial lesions were scattered even beneath the trabeculae carnae or behind the papillary muscles. A few subendocardial fibrosis or structureless fibrosis might also be related with luetic heart disease (Table III).

Diffuse and loose proliferation of the subendothelial connective tissue with scattered lymphocytes in the left ventricular endocardium was observed in 2 cases of subacute bacterial endocarditis (Fig. 17 (b)). Almost similar



(a) (b) (c)

Fig. 17. Endocardial fibrosis due to endocarditis.

(a) Chronic rheumatic endocarditis. Markedly thickened endocardium is lost primary structure with capillary invasion and cellular infiltration in deeper layer.

Elastica van Gieson's stain. 40×

(b) Subacute bacterial endocarditis. Subendothelial fibrosis with increased cellular component.

Elastica van Gieson's stain. 100×

(c) Parietal endocarditis of unknown origin. Irregularly arranged collagen fibers and cellular infiltration.

Elastica van Gieson's stain. 100×

but more localized lesion was also found in rheumatic heart disease.

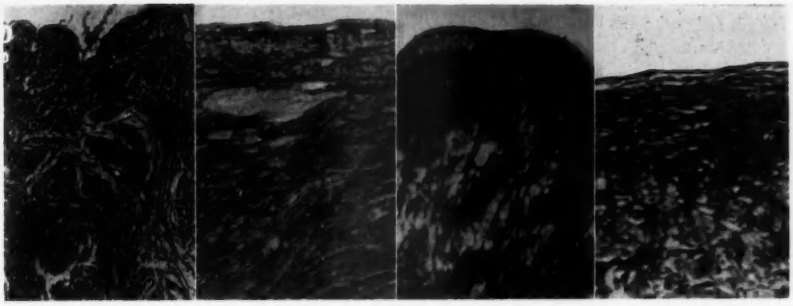
A case with suspected congenital aortic stenosis showed a non-specific parietal endocarditis with diffuse lymphocytic, monocytic and plasma cellular infiltration in the irregularly arranged collagen fibers in the left ventricle (Fig. 17 (c)). A case of acute bacterial endocarditis had several mural vegetations which consisted of localized abscess in the endocardium.

Generally speaking, endocardial thickening due to endocarditis had no significant relationship with myocarditis but rather had some relationship with valvular lesion. If the endocardial fibrosis was a remnant of endocarditis, the fibrosis had to have commonly localized or patchy distribution and miscellaneous histological type with irregularly arranged collagen fibers or elastic fibers. Diagnosis of this type of fibrosis became more rational if there were some chronic or recurrent inflammatory signs in the endocardial fibrosis.

(7) Endocardial fibrosis of miscellaneous origin:

(a) Parietal endocardium of collagen disease other than rheumatic fever frequently appeared whitish. A heart with periarteritis nodosa showed subendocardial cellular infiltration as well as perivascular infiltration. A successive subendocardial fibrosis distributed rather predominantly at the

inflow tract of the left ventricle (Fig. 18 (a)). Almost same process was observed in endocardium of a case with lupus erythematodes.



(a) (b) (c) (d)

Fig. 18. Subendocardial fibrosis of miscellaneous origin.

(a) Periarteritis nodosa. Subendocardial cellular infiltration. Elastica van Gieson's stain. 100×

(b) Interstitial myocarditis. Subendocardial fibrosis with remnant of elastic layer. (This case was from the Medical Examiner's Office of Tokyo.) Elastica van Gieson's stain. 400×

(c) Amyloidosis. Subendocardial deposition of PAS positive substance. PAS stain. 400× (This case was from the 3rd Dept. of Int. Med., Univ. of Tokyo.)

(d) Gargoylism. Subendocardial deposition of special substance. PAS stain. 400× (This case was from the Mitsuikosei Hospital.)

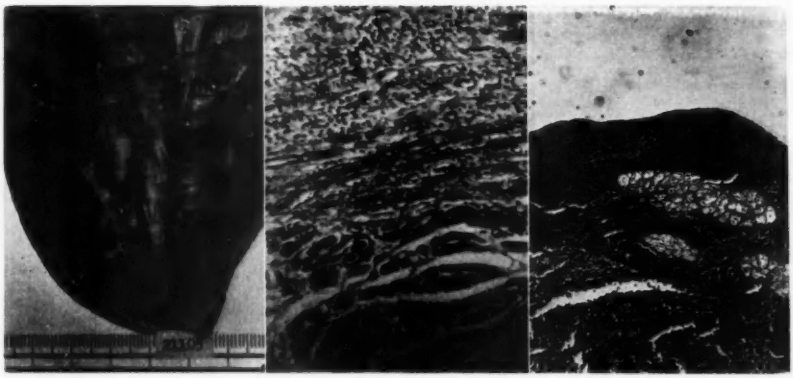
(b) A case of giant cellular myocarditis with diffuse subendocardial fibrosis which was assumed as a result of subendocardial inflammation was also observed (Fig. 18 (b)).

(c) Amyloidosis (Fig. 18 (c)) and gargoylism (Fig. 18 (d)) had some special substance deposited in the subendocardial connective tissue and caused successive fibrosis. In these hearts, the parietal endocardium appeared macroscopically whitish.

(d) Leukemic infiltration into the parietal endocardium was accompanied by a diffuse fibroplastic process, and occasionally it might resemble endocarditis parietalis fibroplastica (Löffler) (Fig. 19 (a), (b)).

(e) Subendocardial bleeding was seen in cases of aplastic anemia (Fig. 19 (c)), leukemia (2/6), malignacy (5/22), liver cirrhosis (2/17) and heart disease (1/25), up to 8.5% of the total cases studied.

(f) A specific heart disease with marked diffuse endocardial fibrosis such as endocardial fibroelastosis[9], endocarditis parietalis fibroplastica,[6] endomyocardial fibrosis[7] and endomyocardial sclerosis[8] will be discussed in the next report.



(a) (b) (c)

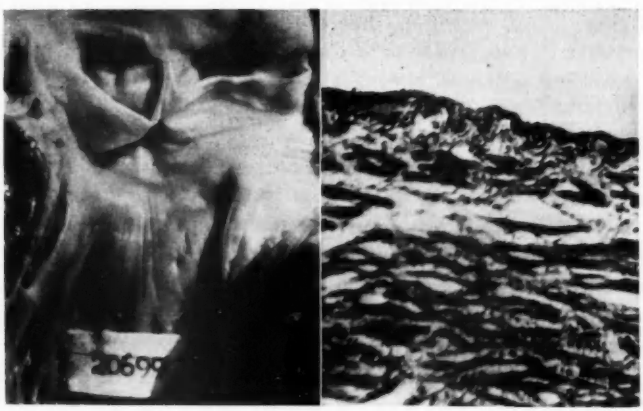
Fig. 19. Heart of blood disease.

(a) Monocytic leukemia. Whitish irregular thickening of endocardium of the left ventricle.

(b) Diffuse leukemic infiltration in the endocardium with increased collagen fibers. Elastica van Gieson's stain. 100× (This case was from the Dept. of Int. Med. and Physicotherapy, Univ. of Tokyo.)

(c) Aplastic anemia. Bleeding into the endocardium. Elastica van Gieson's stain. 40×

(8) False thickening of the parietal endocardium: Marked atrophy of the myocardium brought about a waving of endocardium, selectively of



(a) (b)

Fig. 20. False thickening of endocardium.

(a) Sarcoma. Whitish discoloration of the outflow tract of left ventricle.

(b) Marked waving of elastic layer of the endocardium. Elastica van Gieson's stain. 100×

the elastic layer (Fig. 20 (b)). The endocardium appeared relatively thickened up to 100 μ, but it was not a real thickening. The geographical distribution of the false thickening of the endocardium showed the normal pattern, and this type of endocardial change could be recognized even macroscopically by the feature of the fine wrinkles on the endocardial surface (Fig. 20 (a)). The weight of the hearts with the false thickening of the endocardium (231 Gm.) was statistically smaller than that of the hearts with the normal endocardium (268 Gm.). As a matter of fact, this phenomenon was most frequently observed in the hearts of malignant tumor with cachexia (55%, 12/22).

Presentation of a New Classification of the Abnormally Thickened Parietal Endocardium—

Classification of the abnormal endocardium can be made from the morphological standpoint and the causal-genetic standpoint.

A. The classification of parietal endocardial thickening on the morphological basis (Fig. 21):

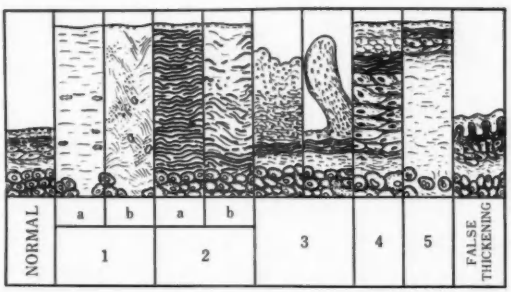


Fig. 21.

(1) structureless fibrosis.
  (a) homogenous type.
  (b) irregular type.
(2) fibroelastosis.
  (a) homogenous type.
  (b) irregular type.
(3) thickening of subendothelial layer.
(4) thickening of all of the 5 layers.....elastomyofibrosis.
(5) thickening of subendocardial layer.
((6) false thickening.)

B. The classification on the causal-genetic basis:
(I) thrombogenic type.

(i) postnecrotic.
(ii) inflammatory.
(iii) miscellaneous.

(II) hypertrophic and / or hyperplastic type.
(i) mechanically stimulated.
(ii) abnormally reacted.

(III) exudative, edematous or deposited type.
(i) inflammatory.
(ii) due to altered membrane permeability.
(iii) related to metabolic disturbance.
(iv) due to deposition of some special substance.

(IV) congenital type.

Table IV. Correlation between Morphological and Genetic Classification of Endocardial Fibrosis

Morphological classification	Causal-genetic classification	Process to fibrosis	Example
Structureless fibrosis	← Thrombogenic	Organization of thrombus.	Anoxic state of endocardium. Myocardial infarction.
	under special condition	Induced from any type of fibrosis by dilatation of chamber or distension of endocardium.	Endocarditis. Leukemic infiltration. Jet lesion. Cardiac dilatation. Ventricular aneurysm.
Fibroelastosis	← Congenital	Developmental anomaly of Bulbus cordis.	Foetal endocardial fibroelastosis.
Subendothelial fibrosis	← altered reactivity	Altered sensitivity and reactivity of endothelium and subendothelial layer.	Allergic endocarditis. SBE. Rheumatic endocarditis.
	Hyperplastic		Endocardial pocket.
	Hypertrophic	Jet impact of blood-stream with oblique direction.	Simple subendothelial hyperplasia.
Elastomyofibrosis	← mechanical stimulation	Compensatory process. Friction zone of blood stream. Increased blood pressure.	Hypertension. Aortic insufficiency.
Subendocardial fibrosis	Exudative ← Edematous Deposited	Acellular slowly progressive fibrosis successive from edema or deposition of special substance. Subendocardial inflammation.	Endokardose. Anemia. Amyloidosis. Gargoylism. Collagen disease.

Correlation between these 2 types of classification is shown in Table IV. When these 2 types of classification were applied to the endocardial thickening, many clinico-pathological problems on the previously described intracardiac lesion might be resolved.

(1) The structureless endocardial fibrosis might usually be resulted from

organization of mural thrombus on destructed endocardium. Myocardial infarction (postnecrotic), endocarditis (inflammatory) and impact of strong jet stream (miscellaneous) destructed normal endocardium, and thereafter the thrombogenic fibrosis of the endocardium occurred. Therefore, the structureless endocardial fibrosis was considered to exhibit the terminal stage of reparative process of destructed endocardium. In the initial stage, the fibrosis had vascular invasion and cellular infiltration, but in the later stage, it transformed to the homogenous fibrosis without vascularisation or cellular infiltration. About the fibrosis resulted from endocarditis, the diagnosis could be made easily in the initial stage due to its marked irregularity of arrangement of collagen fibers, but it became difficult to make diagnosis in the later stage since the irregular collagenosis was taken place by homogenous non-specific structureless fibrosis. The same tendency was observed in the case of myocardial infarction. Extremely complicated endocardial fibrosis was observed frequently in the case with chronic recurrent endocarditis such as rheumatic fever. In such a case, as demonstrated in Fig. 17 (a), regularly arranged collagen fibers were mingled with irregularly arranged ones with inflammatory sign.

The structureless fibrosis might be partly resulted from other causes than the thrombogenic origin. When the apparently normal superficial layer of subendocardial fibrosis degenerated and disappeared, the structureless endocardial fibrosis might be completed from the subendocardial fibrosis. The structureless type of fibrosis might be resulted from miscellaneous types of endocardial lesions in the terminal stage. The author had, however, no experience that subendothelial fibrosis or elastomyofibrosis transfromed to the structureless fibrosis.

(2) Typical endocardial fibroelastosis was seen in the foetal endocardial fibroelastosis which was assumed to be of congenital origin. Acquired fibroelastosis was considered to have developed from the structureless fibrosis under certain special condition. When rhythmical distention has been acting on the endocardial scar tissue for sufficiently long time such as more than 6 months, increased elastic fibers were found in the endocardial fibrosis (Fig. 13 (b), Fig. 14). In fact, this type of fibroelastosis appeared remarkably in the wall of ventricular aneurysm or in the wall of markedly dilated ventricle. Much attention should be paid to the fact that the fibroelastosis was established when the normal structure of endocardium was lost. But a few exception was observed, too. The increase in elastic fiber was sometimes recognized in the subendocardial fibrosis if it persisted for a sufficiently long time. Whether the fibroelastosis was homogenous or not could be determined by the presence or absence of recurrent distortion or destruction of the established fibroelastosis. Much of the fibroelastosis showed homogenous type with regular arrangement of elastic fibers oriented parallel to the lumen, but a few instances with chronic

recurrent endocarditis such as rheumatic fever (Fig. 17 (a)) had the distorted or split elastic fibers. If sufficiently long term elapsed from the establishment of fibroelastosis, irregular type of the fibroelastosis might transform to homogenous and regular type. The time factor to establish the fibroelastosis is indicated in Fig. 14 (b). It needed more than 6 months to establish the fibroelastosis either from the case of myocardial infarction or from the case of endocarditis. As a special instance, some elastic fibers inceased only in the superficial layer of the endocardial pocket. It was considered that the site where elastic fiber increased received the strongest strain from jet stream.

(3) The subendothelial fibrosis consisted of 2 types; the localized type and diffuse type. The endocardial pocket (Fig. 7) and endocardial fibrosis due to localized endocarditis belonged to the former (Fig. 16). In the case of subacute bacterial endocarditis, the diffuse type of subendothelial fibrosis was observed (Fig. 17 (b)). The pathogenesis of the subendothelial fibrosis was usually considered to be thrombogenic. The thrombus deposited on the slightly damaged endocardium which maintained the normal structure at the basis beneath the elastic layer, then, the thrombus was organized and the thrombogenic fibrosis appeared. The trivial damage of superficial endocardium would be due to the impact of jet stream with oblique direction to the wall, endocarditis of slight degree and hypersensitive state of endothelium resulted from allergy or other chemical stimulation. Fig. 6 (a) showed fibrin deposition on the apparently normal endocardium. In such cases, the abnormal coagulability of blood might also play a role to build up the subendothelial fibrosis.

An attention should be given to primary overgrowth of subendothelial connective tissue due to slight mechanical stimulation to the subendothelial mesenchymal cells or hypersensitive reaction of them, as a part of pathogenesis of this type of endocardial fibrosis.

(4) The endocardial elastomyofibrosis maintained the 5 layers of the normal endocardium, but they were markedly hypertrophic or hyperplastic. Among them, the smooth muscle layer was thickened most remarkably, and its thickness had a correlation with previous hypertension (Fig. 9). The pathogenesis of this type of endocardial thickening might be concerned with an increased intracardiac pressure and a friction effect of ejecting blood stream from the left ventricle. But it appeared that the elastomyofibrosis was neither related to previous endocardial destruction nor to thrombogenic origin in its pathogenesis. The friction effect of blood stream might cause a strain in the endocardium, and brought about hypertrophy and hyperplasia of smooth muscle layer as well as other layers. Anemic state might promote this change. These findings have prompted the author to designate this elastomyofibrosis as "friction zone".

The mechanical stimulation of blood stream might cause several types

of endocardial fibrosis. The impact of strong jet stream with vertical direction to the wall was considered as a cause of the structureless endocardial fibrosis. That with oblique direction caused the endocardial pocket and the simple subendothelial fibrosis. These 2 types of mechanical lesion were mentioned as "jet lesion." The friction effect of jet stream with parallel direction to the wall caused "friction zone."

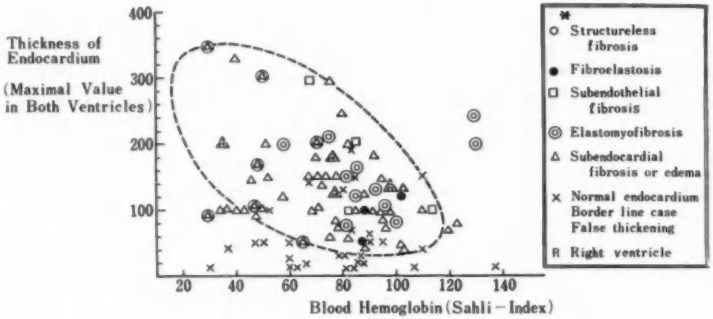
(5) The subendocardial fibrosis was assumed as a terminal form resulted from miscellaneous changes in the subendocardial space. Inflammation, exudative process, edema or invasion of a plasma component and deposition of some special substance might be main causes of subendocardial fibrosis. The subendocardial inflammation was observed usually in rheumatic heart disease and periarteritis nodosa. Abnormal membrane permeability due to anoxia of endocardium might be responsible to a subendocardial exudative process without cellular reaction. Cases with general metabolic disturbance, such as liver cirrhosis and uremia, had marked subendocardial edema. Amyloidosis, gargoylism and other disease with metabolic abnormality exhibited subendocardial deposition of special substance or metabolite, respectively. The successive fibrosis from these miscellaneous changes except that due to endocarditis, was considered as "endocardosis."

Whether subendocardial myocardial degeneration or necrosis was responsible for subendocardial fibrosis or not, was difficult to determine. So-called subendocardial infarction usually preserved several layers of muscle fibers right beneath the endocardium, and in this case, overlaid endocardium commonly maintained the normal structure. When the destruction of myocardium involved overlaid endocardium, the structureless endocardial fibrosis or fibroelastosis appeared. On the other hand, myocardial degeneration due to metabolic disturbance had no special preponderance in the myocardium just beneath the endocardium. Therefore, subendocardial fibrosis which maintained normal endocardial structure in the superficial layer, would be rarely compatible with subendocardial myocardial fibrosis. Generally speaking, the subendocardial myocardial fibrosis was usually accompanied by the structureless fibrosis or fibroelastosis of endocardium.

Considerations about Several Factors Concerning the Degree of the Endocardial Thickening—

Above mentioned consideration was limited to the qualitative aspect of 5 types of endocardial thickening. The quantitative appraisal of endocardial thickening is tried in this chapter.

(1) The role of anemia to endocardial thickening was disclosed in Fig. 22. Simple anemia was not always incompatible with normal endocardium. There were 9 cases with normal endocardium in the severe anemic group with hemoglobin index of less than 60%. However, the thickening of pathological endocardium was more remarkable in the anemic group. Therefore,



* These symbols are common in the following figures.

Fig. 22. Endocardial thickening and anemia, excluding endocardial thickening due to endocarditis, postnecrotic fibrosis and jet lesion.

it might be assumed that anemia was a factor to accelerate the thickening process of pathological endocardium, above all, in the endocardosis and elastomyofibrosis. But, it was difficult to determine which was effective on the endocardial thickening, anemia or metabolic disturbance, since the grade of anemia might be a reflection of the severity of metablic disease.

(2) No apparent correlation between heart weight and thickness of endocardium was proved in general, but the hypertrophied heart of more than 500 Gm. never had normal endocardium. A gross relationship between heart weight and the grade of elastomyofibrosis was recognized among the heart of the hypertensive group, in the range of 300 Gm. to 600 Gm., (Fig. 23 (a)).

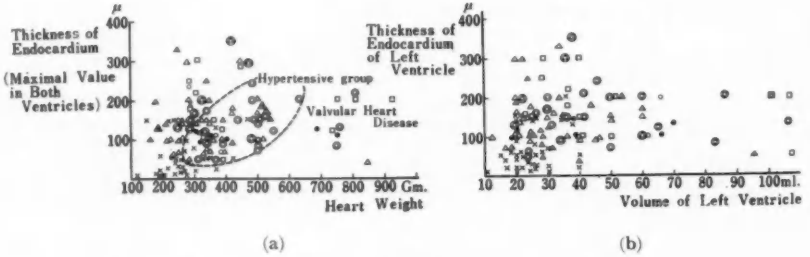


Fig. 23.

(a) Endocardial thickening and heart weight, excluding endocardial thickening of localized nature, for example endocarditis, jet lesion etc.

(b) Endocardial thickening and cardiac dilatation, excluding endocardial thickening of localized nature.

(3) Cardiac dilatation, estimated as the volume of left ventricle, had no significant relationship with thickening of endocardium. On the other

hand, the left ventricular dilatation of more than 40 ml. was incompatible with normal endocardium (Fig. 23 (b)). The endocardial elastomyofibrosis and fibroelastosis was proved frequently in the dilatation group.

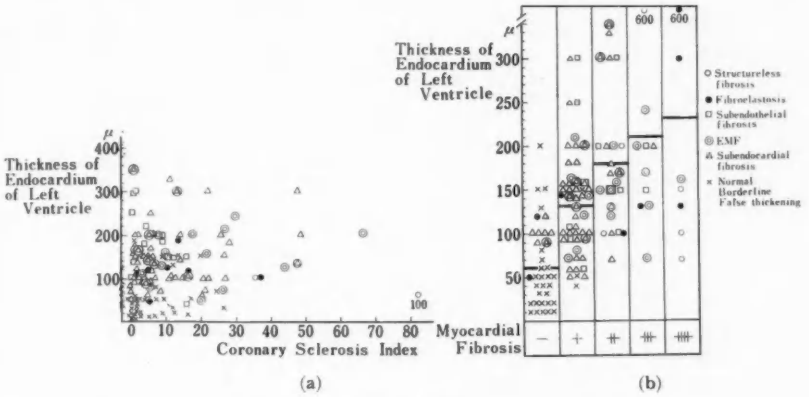


Fig. 24.

(a) Relationship between endocardial thickening and coronary sclerosis, excluding endocarditis and jet lesion.

(b) Relationship between endocardial thickness and myocardial fibrosis.

(4) Fig. 24 (a), indicates relationship between coronary sclerosis index and thickness of left ventricular endocardium. The coronary sclerosis showing more than 30 in the sclerosis index was incompatible with normal endocardium, and the same evidence between endocardial thickening and the aortic sclerosis index of more than 40 was recognized. It was suggested that endocardial fibrosis was related with myocardial insufficiency resulted from coronary sclerosis as well as with myocardial infarction.

(5) Apparently significant relationship between myocardial fibrosis and endocardial thickening is shown in Fig. 24 (b). The degree of myocardial fibrosis was divided as: none (−), mild (+), moderate (++), severe (+++), or extremely severe (+++). The degree of myocardial fibrosis was significantly parallel with endocardial thickening. Moreover, no normal endocardium was present in the group of myocardial fibrosis of more than grade (++), and the structureless endocardial fibrosis or fibroelastosis was frequently observed in the extremely severe myocardial fibrosis.

(6) The thickness of pathological endocardium commonly had no marked correlation with thickness of the aortic valvular leaflet except the thickness of elastomyofibrosis.

(7) Thrombogenic type was most frequently observed in the pathogenesis of endocardial fibrosis. The author examined macroscopically thrombus formation on the parietal and valvular endocardium. The thrombosis was

Table V. Incidence of Thrombus Formation on the Endocardium

	Number of cases	Endocardial thrombosis	Incidence of thrombosis	Site of thrombosis*				
				Left Vent.	Right Vent.	Left Atr.	Right Atr.	Valve M: Mitral A: Aortic T: Tricuspid
Sclerotic heart d. Hypertensive h. d.	17	6	35%	6	0	1	0	0
Valvular heart d.	25	12*	48	5*	1*	4	1	M 4 A 3* T 1
Chronic nephritis	11	0	0	0	0	0	0	0
Pulmonary disease	9	3	33	1	0	0	2	0
Liver cirrhosis	17	2**	12	1**	1	1	1	M 1 T 1**
Malignant tumor	22	6	27	2	1	3	4	A 1
Blood disease	6	1	17	1	0	1	1	0
Others	10	2	20	2	1	0	0	0
Total	117	32	27%	18	4	10	9	11

* Including 2 cases of subacute bacterial endocarditis.
** Including 1 case of acute bacterial endocarditis due to Klebsiella-septicemia.

observed in 27% of a total of 117 cases. Among them, there were 12 cases of valvular heart disease including 2 cases of subacute bacterial endocarditis, 4 with coronary sclerosis, 1 with atypical verrucous endocarditis and 14 with non-bacterial thrombotic endocarditis. The non-bacterial thrombotic endocarditis was observed chiefly in the malignant tumor group and other wasting diseases (Table V), and 12 out of 14 cases of this group had thrombus-formation on the parietal endocardium.

(8) Table VI (a) showed that the geographical distribution of thickened endocardium was characteristically concerned with the histological type of endocardial fibrosis. Most types of fibrosis had a preponderant site of thickening at the outflow tract of both ventricles. However, the subendocardial fibrosis that consisted chiefly of endocardosis, exhibited frequently preponderance of inflow tract or equality of inflow and outflow tract of both ventricles (50% in the left ventricle, and 80% in the right ventricle). Endocardial fibroelastosis and structureless fibrosis had essentially no preponderant site.

(9) The incidence of pathological endocardial thickening was 74% among

Table VI. (a) Relationship between Histological Type and Geographical Distribution of Endocardial Thickening

	Total	Left ventricle			Right ventricle		
		0>I*	0=I	0<I	0>I	0=I	0<I
Normal or Border line case	32	27 (84%)	5 (16%)	0 (0%)	17 (53%)	14 (44%)	1 (3%)
Subendocardial fibrosis	47	25 (53)	18 (38)	4 (9)	10 (21)	25 (53)	12 (26)
Elastomyofibrosis	28	28 (100)	0 (0)	0 (0)			
Subendothelial fibrosis	16	14 (88)	1 (6)	1 (6)			
Structureless fibrosis	3	2 (67)	1 (33)	0 (0)			
Fibroelastosis	7	4 (57)	0 (0)	3 (43)			

Endocardial thickening:
* 0>I; predominant at outflow tract.
0=I; equal at outflow and inflow tract.
0<I; predominant at inflow tract.

(b) Pathological Thickening of Parietal Endocardium Its Standard and Incidence

Left ventricle: over 100 μ Left atrium: over 1,000 μ
Right ventricle: over 50 μ Right atrium: over 500 μ

Case	Number of cases	Pathological thickening of endocardium	Incidence
Hypertensive, sclerotic heart d.	17	16	94%
Valvular heart disease	25	24	96
Chronic nephritis	11	9	82
Liver cirrhosis	17	12	70
Malignant tumors	22	10	46
Pulmonary disease	9	9	100
Blood disease	6	2	33
Others	10	6	60
Total	117	88	74%

the total of 117 examined hearts with various diseases, if the thickness more than 100 μ at the left ventricle, more than 50 μ at the right ventricle, more than 1,000 μ at the left atrium and more than 500 μ at the right atrium in the parietal endocardium were assumed as standard of pathological thickening of endocardium (Table VI (b)).

Comment

It is generally considered that endocardial fibrosis may occur from miscellaneous origin. It has been classically divided to be thrombogenic, functional-elastic and inflammatory by Hertel[10),16)] or to be functional and non-functional as well as to be reparative and compensatory by Fisher and Davis.[5)] From another standpoint, primary and secondary endocardial sclerosis has been classified.[17)] However, most of these classic classifications were too incomplete to analyse endocardial thickenings resulted from various causes.

The author proposed a new classification on the basis of morphology and pathogenesis, and discussed the relationship between these 2 types of classification.

(1) The jet lesion has been classically described by Saphir,[18)] Hellerstein[18)] and Edward[19)] as "endocardial pocket" or "pseudocusp". The pathogenesis of the endocardial pocket has been considered as primary proliferation of subendothelial connective tissue. Mechanical stimulation such as the impact of the jet stream irritated the surface of endocardium, and caused proliferation of collagen fibers followed by increased elastic fibers or even smooth muscles probably developed from mesenchymal cells in the subendothelial layer.[18)] The pocket-form of this lesion was dependent on the direction of the jet stream. Therefore, the systolic and diastolic type of pocket was described by Saphir.[18)] Less attention has been paid to the jet lesion other than the endocardial pocket.

The author observed the structureless endocardial scar with overlaid organizing thrombus as a jet lesion (Fig. 5). It was sometimes very difficult to differentiate this lesion from the remnant of endocarditis, especially in luetic heart disease. The pathogenesis of this endocardial scar might be thrombogenic. The organization of the thrombus which deposited on the endocardium damaged by the impact of the jet stream, might develope to the homogenous endocardial scar. The endocardial pocket could be found only in the case of aortic regurgitation and mitral insufficiency. This exhibited that the endocardial pocket needed not only the oblique direction of the jet stream but a considerable pressure gradient between two chambers for its pathogenesis. In the initial stage of this lesion, organizing fibrin thrombus was observed on the apparently normal endocardium, with sharp limitation towards the source of jet stream (Fig. 6). In the later stage, the superficial layer of the endocardial pocket consisted of looser connective tissue and the basal layer had dense collagen tissue, and sometimes fibrin thrombus on the surface of the pocket was also observed (Fig. 7). In the terminal stage, the endocardial pocket consisted of homogenous collagen fibers and increased elastic fibers appeared in the superficial layer. The normal elastic layer was always present at the basal layer of

the pocket in all of the examined cases. These findings prompted the author to consider the pathogenesis of this lesion is due to thrombogenic origin. Neither vascular invasion nor cellular infiltration in this lesion was compatible with thrombogenic origin if the pocket was sufficiently old. Even the fibrosis of inflammatory origin showed sometimes homogenous structureless scar, if it persisted sufficiently long time. The increase in elastic fibers in the superficial layer of the pocket exhibited a new formation of elastic fibers in the area receiveing the strongest strain, and was compatible with thrombogenic origin. Therefore, the author considered that thrombogenic origin might be playing main role in establishing the endocardial pocket, but the simple overgrowth of the connective tissue might also play a role occasionally. The simple hyperplasia of the subendothelial connective tissue layer was observed as a jet lesion in the area where the weak jet stream struck with either vertical or oblique direction. Usually this lesion was not limited so sharply but showed rather diffuse fibrosis. The pathogenesis of this lesion was considered as thrombogenic origin or simple overgrowth of subendothelial layer.

(2) Fisher and Davis[5] has considered that the endocardial elastomyofibrosis might exhibit a functional or compensatory endocardial thickening due to mechanical stimulation and it might be related to cardiac hypertrophy or dilatation.[5],[19] The pathogenesis of this lesion was assumed to be due to a persistent hypertension,[17] mechanical irritation or friction effect of ejecting blood steam[1] as well as sclerosing process similar to the intimal sclerosis of vessels.[18]

The correlation between the degree of elastomyofibrosis and the degree of previous hypertension was more strict than that between the elastomyofibrosis and cardiac hypertrophy or dilatation (Fig. 9). The heart weight and ventricular volume which indicated a gross correlation with the elastomyofibrosis, might be a sort of parameters of hypertension (Fig. 24). The elastic layers in the endocardial elastomyofibrosis exhibited some thickening as well as the smooth muscle layer, but the degree of the former was less closely related to the hypertension than the latter. The pathogenesis of this lesion might be concerned with increased intracardiac pressure and friction effect of ejecting blood. The friction effect was most markedly exhibited at the outflow tract of left ventricle when the interventricular septum was hypertrophied. The "friction zone" has been sometimes applied to the jet lesion, but the author proposed that the "friction zone" should be limitedly applied to the endocardial elastomyofibrosis.

(3) "Endokardose" has been used at first by Lange.[15] He has described Endokardose as subendocardial edema, but has not clarified its pathogenesis. On the other hand, myocardial change due to metabolic disturbance chiefly related to dysproteinemia has been described by Wuhrmann,[14] and it was mentioned as Myokardose. Endocardial change due to general

metabolic disturbance consisted of subendocardial edema or successive fibrosis with peculiar type of Lambl's excrescence on aortic valvular leaflets. The author considers that this endocardial change should be called as "Endokardose or endocardosis". The evidence that there was apparent relationship between subendocardial thickening and serum albumin level (Fig. 11), exhibited that the pathogenesis of endocardosis was related to the disturbance of protein metabolism. The subendocardial edema was more marked in the case with short clinical course such as uremia and the subendocardial fibrosis was more pronounced in cases with long clinical course such as portal liver cirrhosis. The endocardosis had some relation with myocardial degeneration, but no apparent relationship with subendocardial necrosis described by Still and Boulet[23] or with mucopolysaccharide degeneration of myocardium.[24] There was no specific PAS positive substance in the subendocardial space or endocardium itself of the hearts in liver cirrhosis or uremia.

In pulmonary disease such as pulmonary tuberculosis, the subendocardial edema was observed in the right side of the heart. However, it was difficult to decide whether this change was related to metabolic disturbance through pH change of the blood or anoxemia due to dyspnea, or not.

Moderate subendocardial fibrosis appeared in amyloidosis and gargoylism (Fig. 18). Case reports about gargoylism,[25] glycogen storage disease[26] and epiloia[27] with endocardial fibroelastosis have been published. It was suspected that some of them might start with subendocardial deposition of a special substance, developing into successive subendocardial fibrosis, and then the endocardial fibroelastosis was completed by degeneration of the superficial layer which preserved the normal endocardial structure.

A special type of subendocardial fibrosis, moreover, might be established from inflammatory process related to collagen disease (Fig. 18 (a)). It was interesting that the abnormal serum protein fraction appeared in these cases, as well as liver cirrhosis. Miscellaneous inflammatory process in the subendocardial space was frequently followed by subendocardial fibrosis (Table III). In large part of these groups, they were resulted from inflammatory process, but in small part, they might be resulted from endocardosis due to a persistent or repeated decompensated state of original heart disease.

(4) Reparative endocardial fibrosis was most frequently observed by myocardial infarction (postnecrotic). About 50% of myocardial infarction has been reported to have endocardial involvement (Blumer[28]) and hyalinization and calcification in the endocardial fibrosis has been also described (Edmondson and Hoxie[29]). Moreover, a case of diffuse endocardial fibrosis with myocardial infarction had been reported, too.[30] The author recognized that all cases of myocardial infarction involving endocardium had stucture-

less endocardial fibrosis and had partly endocardial fibroelastosis.

(5) The typical fibroelastosis was recognized in the foetal endocardial fibroelastosis[8),31)] which was called as primary endocardial sclerosis,[32)] endocardial dysplasia[33)] and so on. The pathogenesis has been considered mostly as congenital developmental anomaly[31)] or simle hyperlasia of endocardium[34)] but partly as due to anoxia of endocardium,[8),34)] intrauterine infection, collagen disease[35),36)] and so on. The discussion in detail on the congenital fibroelastosis will be commented in the next report. The aquired type of fibroelastosis is discussed here. The adult or adolescent form of endocardial fibroelastosis has been reported by Auld,[37)] Horley,[38)] Panke[39)] and Dyson.[40)] Most of them were accompanied by myocardial fibrosis and some of them were considered as secondary or acquired fibroelastosis. The pathogenesis of them has been asserted as thrombogenic,[40)] as sclerosing process analogous to the vascular sclerosis[40)] or as intoxication through lung,[41)] and other various factors have been considered to be related to the acquired endocardial fibroelastosis. The dilatation factor and time factor were admitted generally as factors to increase elastic fibers in the endocardium, as has already been mentioned in this report (Fig. 14). It was evident that the dilatation of the cavity promoted establishment of the fibroelastosis in the previously destructed endocardium (Fig. 14). A marked dilatation of the cavity might split the normal elastic layer and might establish the fibroelastosis through the structureless endocardial fibrosis. The author indicated that cardiac dilatation was incompatible with normal endocardium, if it increased more than a certain limit (Fig. 23), but in such a case, the pathological endocardium was not always the fibroelastosis. Therefore, it was concluded that the endocardial fibroelastosis was concerned with cardiac dilatation in the pathogenesis, but that the cardiac dilatation did not always bring about the endocardial fibroelastosis.

(6) Rheumatic parietal endocarditis was observed most frequently at the posterior wall of left atrium, as has already been mentioned by von Glahn,[43)] Thayer[44)] and Gross.[45)] Marked fibrous thickening of endocardium with irregular arrangement of collagen fibers and with partly inflammatory signs, has been considered to be characteristic in the chronic recurrent rheumatic endocarditis.[14)] The author observed various histological types and various geographical patterns of distribution of the endocardial fibrosis in rheumatic heart disease. Among them, localized subendothelial hyperplasia and subendocardial fibrosis were most frequently recognized. The subendothelial hyperplasia might be of thrombogenic origin concerned with slight inflammation in the endothelial layer, and the subendocardial fibrosis might be mostly resulted from subendocardial inflammation such as Aschoff's nodule, granulomatous infiltration or non-specific cullular infiltration,[14)] but partly from the endocardosis due to chronic recurrent decompensated state.

The parietal endocarditis of luetic origin has been doubtful in its presence, but a sort of hypersensitive type of luetic endocarditis has been accepted partly.[6] However, it was extremely difficult to differentiate this type of lesion from the jet lesion or the secondary endocardial involvement due to myocardial damage of luetic origin.

The diffuse loose subendothelial fibrosis with relatively rich cellular component in the case of subacute bacterial endocarditis might be resulted from thrombogenic origin or simple overgrowth of connective tissue due to hypersensitive or allergic state of the superficial layer of the endocardium. It is interesting to compare it with the Löffler's second case of endocarditis parietalis fibroplastica[53] which was accompanied by a subacute bacterial endocarditis and was assumed to be an allergic nature in the pathogenesis. (7) There was apparent relationship between endocardial thickening and myocardial fibrosis (Fig. 24 (b)). There were possible 3 courses through which the former and the latter interacted injuriously each other. In the first course, the myocardial insufficiency, which was represented by the degree of myocardial fibrosis, brought about cardiac dilatation, which might cause the secondary endocardial thickening. Fig. 23 (b) showed the evidence that the cardiac dilatation more than a certain limit was incompatible with normal endocardium. By the way, the structureless endocardial fibrosis might develope the endocardial fibroelastosis which had gross correlation with cardiac dilatation. So, at least a part of endocardial thickening such as a secondary or compensatory type,[49] might be related to the myocardial insufficiency through cardiac dilatation. In the second course, the same factor that caused myocardial fibrosis, might act upon the endocardium simultaneously, and it might result in the endomyocardial fibrosis. When the myocardial infarction involved the endocardium, the reparative process might establish the structureless endocardial scar. In the third course, the primary endocardial thickening especially due to thrombogenic origin, might cause occlusion or stenosis of the vascular system communicating between myocardium and cardiac lumen,[31] such as thebesian vein and arterioluminal anastomosis. Such a case that showed this evidence, has been reported by Flynn.[50] The primary endocardial changes might cause subendocardial ischemia and successive fibrosis, because subendocardial muscle fibers received blood supply from cardiac lumen.[51],[52] However, in the most cases with endocardial thickening myocardial damage was not always localized in subendocardium, but was scattered in median or outer layer of myocardium. Therefore, the most cases of endocardial thickening were related to myocardial damage as the compensatory (secondary) and reparative process. The case with primary endocardial sclerosis and secondary myocardial fibrosis, was supposed to be rare. The author showed the evidence that the heart weight, cardiac dilatation and coronary sclerosis were incompatible with normal

endocardium if they increased more than a certain limit (Fig. 23, 24). This evidence might mean a secondary endocardial damage through myocardial insufficiency due to anoxia or hypertrophy of muscle fibers.

(8) Though anoxia of endocardium has been repeatedly insisted as a factor of pathogenesis of endocardial fibrosis, yet severe anemia might be compatible with normal endocardium (Fig. 22). The degree of pathological thickening of endocardium, on the other hand, appeared to be promoted by anemia. Therefore, the anemia might be a promoting factor of pathological endocardial thickening, but not a essential factor to establish endocardial fibrosis.

(9) On the pathogenesis of various types of endocardial fibrosis including a specific endocardial disease (Löffler,[5] Fossel,[46] Davies[6] et al.), the thrombogenic origin was most frequently observed. But few attention has been paid to the thrombus formation on the parietal endocardium. The author observed 14 cases with non-bacterial endocardial thrombosis among a total of 117 cases. About this type of thrombosis which has been considered as a terminal phenomenon of wasting disease,[47] previous description[48] was limited only to valvular thrombosis. The author recognized mural thrombosis in 12 out of 14 cases of non-bacterial endocardial thrombosis. But, it is not clear, whether this type of thrombosis plays a certain role in establishing the parietal endocardial thickening or not.

(10) The geographical distribution of the parietal endocardial fibrosis had a characteristic feature by its histological type. Most of the endocardial fibrosis in left ventricle had a preponderant site at the outflow tract, but the endocardial fibrosis due to endocardosis had, on the contrary, almost equal grade of thickening at the outflow tract and at the inflow tract, or in part, somewhat preponderance of the inflow tract (Table VI (a)). The same tendency was observed at the right ventricle. It was very interesting to remember Davies' description that the strict limitation of endocardial thickening was seen at the inflow tract of both ventricles in his endomyocardial fibrosis in Uganda which was assumed to be concerned with nutritional disturbance in the pathogenesis.

As far as the pathological endocardial thickening is concerned, one must show exactly its localization or distribution and the type of the structural changes in its components, because there is the physiological endocardial thickening, which varies considerably in each case.

(11) The incidence of the pathological parietal endocardial thickening has been reported to be extremely low such as 0.2% among 11,045 autopsied cases[4] or 4 among 115 cases with chronic endocarditis,[3] on the other hand, the other author has reported its considerably high incidence up to 60% among 109 autopsied hearts.[5] In the present study, the pathological thickening of parietal endocardium was found at a very high incidence up to 74% among 117 unselected autopsied hearts.

Severe and diffuse endocardial thickening might show a peculiar clinical syndrome mentioned as "parietal endocardial thickening syndrome" and the author will discuss the clinical problems in cases with markedly thickened endocardium in the next report.

Summary

Macroscopical and microscopical examination of 117 unselected autopsied hearts revealed various degrees of pathological parietal endocardial thickening in 74% of them. The physiological thickening of the normal parietal endocardium was determined as 20 μ at the outflow tract and papillary muscles of the left ventricle, as 10 μ at the inflow tract of the left ventricle, the outflow tract and papillary muscles of the right ventricle, as 7 μ at the inflow tract of the right ventricle, as 300 μ at the posterior wall of the left atrium and as 100 μ at the posterior wall of the right atrium. The parietal endocardium had a tendency to increase its thickness with age.

A new classification of the pathological thickening of parietal endocardium which was made on the morphological and causal-genetic basis was proposed:

A. Morphological classification.
   1. structureless fibrosis.
   2. fibroelstosis.
   3. thickening of subendothelial layer.
   4. thickening of all of the 5 layers.
   5. thickening of subendocardial layer.
   6. (false thickening.)

B. Causal-genetic classification.
   I. thrombogenic type.
   II. hypertrophic and / or hyperplastic type.
   III. exudative, edematous or deposited type.
   IV. congenital type.

The correlation between these 2 types of classification revealed the following evidences:

(1) The endocardial fibrosis resulted from mechanical stimulation of the blood stream consisted of the jet lesion and the friction zone. The former was divided into 2 types and was commonly of thrombogenic origin. The impact of strong jet stream with vertical direction to the wall caused the structureless endocardial scar. On the other hand, the impact of jet stream with oblique direction caused the endocardial pocket or subendothelial fibrosis. The friction zone preserved all of the 5 layers of endocardium, but they were markedly hypertrophied and hyperplastic (Elastomyofibrosis). The pathogenesis of the friction zone was concerned with friction effect of

the blood stream directed parallel to the wall and was related strictly with the persistent hypertension.

(2) The endocardial change due to general metabolic disturbance, exhibited the subendocardial edema or fibrosis (endocardosis), and the degree of this change correlated with the lowering of serum albumin level.

(3) The endocardial fibrosis due to endocarditis showed various histological types, and was mainly circumscribed fibrosis. Subendothelial fibrosis, subendocardial fibrosis or structureless fibrosis were frequently observed. They showed characteristically the irregular arrangement of collagen fibers with chronic inflammatory process.

(4) The myocardial infarction was frequently accompanied with the structureless endocardial scar (reparative fibrosis).

(5) The acquired endocardial fibroelastosis was developed from the fibrosis which lost the primary structure under a certain condition that consisted of mechanical distention and sufficiently long clinical course of more than 6 months.

(6) There was apparent relationship between the grade of endocardial thickening and that of myocardial fibrosis.

(7) The geographical distribution of the endocardial thickening showed commonly the preponderance at the outflow tract of both ventricles. However, some of the endocardosis had a tendency to be preponderant to the inflow tract of both ventricles.

(8) Increase in the heart weight, the grade of cardiac dilatation and the grade of coronary sclerosis was incompatible with the normal endocardium, if they increased more than a certain limit.

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Case Reports

A Case Report of Pulmonary Carcinoma Presenting Superior Vena Cava Obstruction Syndrome —A Rare Case of Bilateral Cardiac Chamber Involvement by Tumor Thrombosis—

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SUPERIOR vena cava obstruction syndrome due to lung cancer is not rare. Much has been written as to the mechanism of the cause of this syndrome but reports on direct involvement of the heart chambers due to cancer growth from the lungs are few. The following case showed not only the penetration of the tumor growth through the superior vena cava into one side of the heart but showed both chamber involvement by extension of another growth through the right pulmonary vein. Although such a widespread lesion could not be determined through clinical manifestations alone, the course of the syndrome was severe and rapid, resulting in comparatively early death.

Case Report

W. O., 64-year-old female, a housewife, had no particular family history. Except for a middle ear surgery performed 27 years ago and a hypertensive condition for the past 3 years, the past history was uneventful.

A low grade fever, cough and dyspnea had been present since March, 1960 and in the end of April an abnormal shadow in the right upper lobe was found in the chest X-ray film. The diagnosis of lung abscess was made and the patient was treated with Chloramphenicol but no improvement was seen. By early part of May severe dyspnea and edema of the face and neck became evident and the patient was referred to us with subsequent hospitalization on May 9th, 1960.

Physical examination on admission revealed a patient of medium stature in fair nutritional state with orthopnea but no asthmatic wheezings were present. The pulse rate of 109 with good tension was observed and the blood pressure was 126/84 mm. Hg. However, a marked swelling of both upper extremities, neck and face was evident and dilated venules were seen on the chest wall showing caudal flow. On the left neck region, a hen-egg sized tender lymph node was found.

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The lung-liver border was in the lower border of the 6th rib on the mid-clavicular line.

The delineation of cardiac dullness on the right side was not clear. The left cardiac dullness was found to be shifted one finger-breadth lateral from mid-clavicular line but no murmurs were heard. The entire right chest was dull on percussion and there spiratory sounds were weak with rhonchi in the right lower base, posteriorly. Liver was palpable 5 finger-breadth below the costal margin and was smooth, soft and elastic. In the left mid-abdominal region, a resistance of an area of a few centimeters in diameter was found tender to palpation. No ascites was present and the spleen and kidneys were not palpable. No edema in the legs was noted and the reflexes were normal.

Laboratory findings revealed RBC count of 4,640,000, Hb. (Sahli) of 83%, color index of 0.9 and WBC count of 4,800 with differential count of 3% eosinophils, 0% basophils, 1% staff, 71% segmented neutrophils, 4% monocytes and 21% lymphocytes. Aside from slight proteinuria, no significant findings in the urine were found. Stool tests were negative. B. S. R. (Westergren) was 65 mm. for the first and 110 mm. for the second hour. Gram positive cocci were found in the sputum but no tubercle bacilli or tumor cells could be seen. Serum biochemical tests showed a total protein value of 6.0 Gm./100 ml. with 44.8% albumin, 13.1% alpha globulin, 13.3% beta globulin and 28.9% gamma globulin with an A/G ratio of 0.81. The NPN was 27.2 mg./100 ml., total cholesterol 234 mg./100 ml., Na 140 mEq./L. and K 4.4 mEq./L.. Meulengracht value of 9, cobalt test of $R_{0(2)}$, T. T. T. of 4.7 and a negative C. C. F. value were seen in the liver function tests. The only abnormal findings in the laboratory data, therefore, were high blood sedimentation values and a reversed A/G ratio.

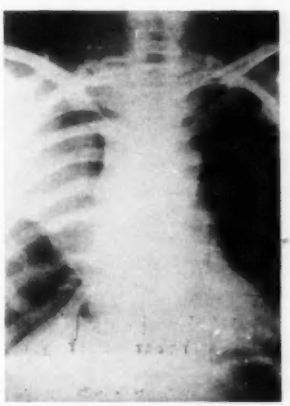

Fig. 1. Chest X-ray.

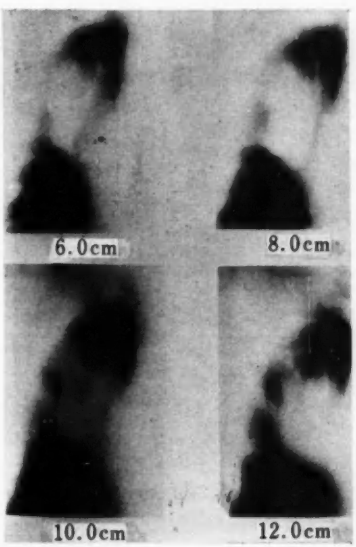

Fig. 2. Right upper tomogram.

In the chest X-ray as well as in the tomograms (Fig. 1 and 2) there were diffuse, dense shadows throughout the upper and middle lobe of the right lung to the hilus. The lower border of this density was clearly defined.

In the ECG findings (Fig. 3), except for a somewhat low voltage and alterations of the R-waves in the chest leads which were believed to be due to respiration, no other marked changes were seen.

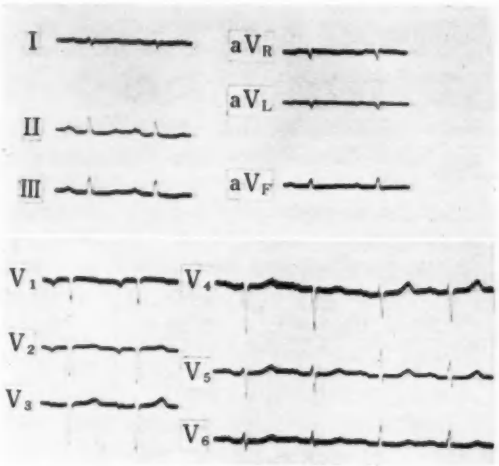

Fig. 3. Electrocardiogram.

Fig. 4. Primary lesion of the right lung.

In the gastro-intestinal tests, irregular contour was seen on the greater curvature of the stomach near the pylorus corresponding to the resistance on palpation.

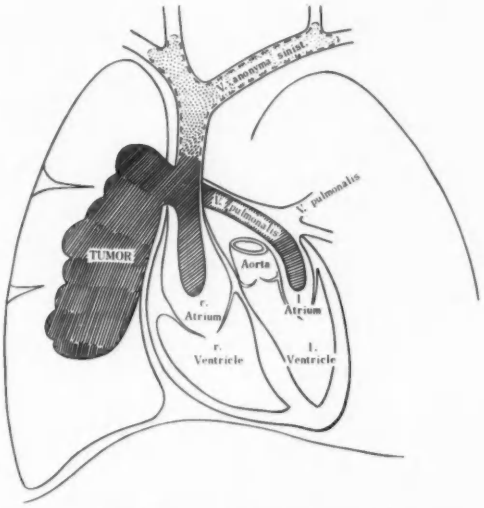

Fig. 5. Schema of the autopsy findings.

Fig. 6. Tumor thrombus hanging into the right ventricle.

Fig. 7. Tumor thrombus hanging into the left atrium.

Course after admission: A diagnosis of superior vena cava obstruction due to lung cancer was made and X-ray therapy and oral thio-TEPA administration were started a week after admission to the hospital. However, the treatments were not effective in stopping the steady increase of dyspnea, swelling of the upper half of the body, cough and dilatation of the veins on the chest. The patient died of respiratory failure on the 25th hospital day.

Postmortem findings: A fist-sized tumor, believed to be the primary lesion, was found near the hilus of the upper lobe of the right lung and a diffuse infiltration over the whole lobe was seen. Both the middle and lower lobes of the right lung were atelectatic and 1,400 ml. of exudate was present in the pleural cavity (Fig. 4). A continuous infiltration to the mediastinal lymph nodes and destruction of the superior vena cava wall resulting in a tumor intervention within the vascular lumen were observed. From the vena cava to the right atrium, this tumor thrombus extended into the right ventricle. From the point of entry of the tumor in the superior vena cava this growth was also seen to have spread up to the jugular veins forming a thrombus (Fig. 5 and 6). A tumor thrombus was also found hanging from the right pulmonary vein into the left atrium (Fig. 5 and 7).

Histologically, the primary tumor showed little interstitial tissues and was a cancer growth composed of spindle type, undifferentiated cells possessing small round nuclei with dense chromatin. A picture of so-called oat cell carcinoma was found (Fig. 8 and 9). Fig. 10 shows the part where the tumor caused destruction of the wall of the superior vena cava and entered the vessel cavity. Fig. 11 is the histological picture of the tumor thrombus (medullary carcinoma) covered with a thin fibrous capsule.

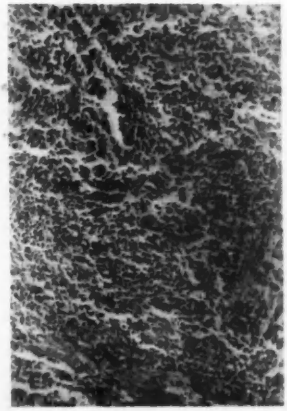

Fig. 8. Oat cell carcinoma of the primary lesion.

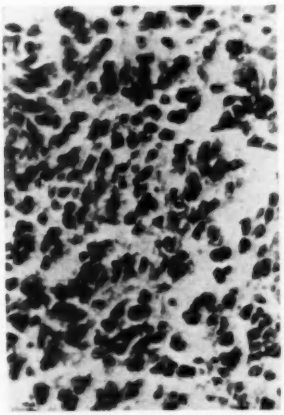

Fig. 9. Oat cell carcinoma of the primary lesion.

Metastasis to the retroperitoneal lymph nodes and those of the portal region and pancreas was also seen and the irregular contour of the pyloric region seen in the X-ray examination of the stomach is believed to have been caused by the metastatic growth in the pancreas.

Fig. 10. The wall of superior vena cava penetrated by the tumor growth.

Fig. 11. Tumor thrombus.

Discussion

As shown by McIntire[1] in 1946 in his report of 524 cases collected from literature and from his own cases, superior vena caval syndrome is not a rare condition. According to his survey the underlying lesions in the majority of the cases are intrathoracic malignant tumors (33.3%), and aortic aneurysms (30.0%). In the former group, malignant lymphoma (39.2%) and malignant bronchial tumor (29.7%) represent over one half of the entire cases (Table I). Eighteen to 17 percent of primary lung cancer has been reported to cause this syndrome[2]-[4] and according to Honma,[4] the lung cancer showing this syndrome is most prevalent in the upper lobe of the right lung and is overwhelmingly dominant in male patients. Histopathologically, this syndrome is seen frequently in the case of squamous cell carcinoma and undifferentiated cell carcinoma but is relatively uncommon in adenocarcinoma.

The mechanism producing vena caval syndrome is generally attributed to the pressure of the tumor against the outer wall of the superior vena cava with the resultant formation of thrombus within the vascular lumen. However, a direct right cardiac chamber involvement by the tumor after penetration of the vena caval wall with a tumor thrombus formation producing this syndrome as shown in the present case is considered exceedingly rare. Moreover, in the present case, the left atrial chamber involvement of the tumor thrombus through the right pulmonary vein caused pulmonary circulatory disturbances which indirectly

Table I. Obstruction of the Superior Vena Cava (McIntire)

(1) Case reports in literature to 1946

Date	Source	No. of cases
1903	Hume	12
1904	Fischer	252
1904~1910	Rauth	43
1911~1921	Dana	44
1922~1933	Ehrlich	60
1934~1946	McIntire & Sykes	113
		524

(2) Basal disease

502 Cases

Primary malignant tumor of the thoracic cavity	33.3%
Aneurysm	30.0%
Chronic mediastinitis	15.4%

Primary malignant tumor of the thoracic cavity (74 cases)

Malignant lymphoma	39.20%
Malignant tumor of lung and bronchus	29.70%
Sarcoma	9.45%
Malignant tumor of thymus	6.75%
Leukemia	4.07%
Malignant tumor of esophagus	1.35%
Chorionepithelioma	1.35%
Undetermined	8.13%

aggravated the systemic circulatory disturbances. The resultant effect was respiratory failure.

Although 10 to 30% of lung cancer present metastasis to the heart, according to Tsuda[5] (Table III), metastasis in form of involvement of the heart chamber due to tumor thrombus is extremely rare and literature shows that among the relatively few contributors of reports on this condition are Toh,[6] Aoki,[7] Tsuda,[5] Adachi,[8] Geipel,[9] Rosenbloom,[11] Cruz and Stambaugh[12] (from superior vena cava to the right chamber), Henke,[10] McDonald et al.,[13] and Mead[14] (from pulmonary vein to the left chamber).

Hanfling[15] reports a 18.3% cardiac metastasis of malignant tumors (127 cases from 694 autopsy cases) but only one case was found to show cardiac chamber involvement. Right chamber involvement of tumor thrombus through the superior vena cava aside from lung cancer was seen in thyroid cancer,[16],[17] and similar right heart involvement via the inferior vena cava was reported in hypernephroma,[18],[19] hepatoma,[20] and testicular carcinoma[21] but these cases are believed to be extremely rare when compared to those arising from lung cancer. However, the direct involvement of both the right and left cardiac chambers simultaneously

Table II. Superior Vena Cava Obstruction in Primary Cancer of the Lung

(1) Incidence

	Total	No. of cases	
Steinberg (1952)	100	17	17.0%
Roswit (1953)	340	51	15.0%
Honma (1959)	208	36	17.3%

(2) Site of lesion (Honma)

Right upper lobe	16
Right middle lobe	3
Right lower lobe	2
Right main bronchus	2
Trachea	1
Left upper lobe	7
Left lower lobe	5
Total	36

(3) Sex (Honma)

	Male		Female
Carcinoma of the lung	169	:	39
	(4.3	:	1)
Superior Vena Cava Obstruction	34	:	2
	(17	:	1)

(4) Histologic type of carcinoma (Honma)

Adenocarcinoma	13	(10%)
Small-cell carcinoma	15	(27%)
Squamous-cell epithelioma	8	(25%)

Table III. Incidence of Cardiac and Pericardial Metastasis from Cancer of the Lung (Tsuda)

Total	Pericardium	Heart	Author
400	23%	16%	Miyaji
	17~30%	15~22%	Tanner
3047	12.7%		Ochsner
234	11.1%		Engerman
4732	13.1%		Ochsner
74	41.9%		Arkin
125	12.0%		Koletsky
40	5.0%		Sumpson
192	30.7%		Tenzel
808	2.7%		Miller
44	11.4%		Mulliqan

through the superior vena cava and pulmonary vein has not been described in literature within our knowledge.

Summary

(1) A 64-year-old woman with primary carcinoma of the right lung presenting superior vena caval syndrome was discussed.

(2) The syndrome was caused by the tumor thrombus hanging into the right atrial and ventricular cavity from the superior vena cava through continuous infiltrative growth from the primary lesion.

(3) A tumor thrombus was also seen to pass through the right pulmonary vein into the left atrial chamber in a similar manner.

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A Case Report of Endomyocardial Fibrosis

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and Hideo UEDA, M.D.*

WHEN marked cardiac enlargement is found in a patient without sufficient evidences to elucidate the condition, its etiology becomes obscure. Infrequently, one can find such cases with obscure cardiopathy among a variety of cases of heart disease. In recent years obscure cardiopathy has attracted the attention of the physicians, and attempts have been made to classify the clinical and pathological features of such diseases. Among various features of such obscure cardiopathy, endomyocardial fibrosis is a peculiar disease because it is a common cause of heart failure in Africans at Uganda. The clinical and pathological features of endomyocardial fibrosis have been thoroughly described in several papers from Uganda.[1)-5)] In the present paper, a case of endomyocardial fibrosis in Japan is reported and its clinical and pathological features are described.

Case Report

A 30-year-old joiner was admitted to the Second Department of Internal Medicine, Tokyo University Hospital, on July 16, 1960 with the chief complaints of exertional dyspnea and palpitation. The family history was noncontributory. The growth of the patient was normal in childhood, and never suffered from any noteworthy diseases. There was a history of occasional alcoholic beverages intake in moderate amounts but no history of smoking. He had been working as a ioiner without any difficulties until the development of the present illness.

At the end of March 1960, the patient caught cold associated with cough and moderate fever of one week duration. About one month later, the nonproductive cough recurred, then the appearance of edema on the face and pretibial region was noticed. From that time palpitation and short breath became noticeable even at his routine work. These symptoms gradually increased in severity. The patient finally consulted a physician, and was told that he had an enlarged heart and swelling of the liver. The treatment with digitalis and theophyllin choline was given for a week with a slight improvement of the symptoms, but he had scarcely returned to his work when he was confined to the bed from the middle of May. About 2 weeks prior to the present admission he had a nonexertional dyspnea and pretibial edema for which some diuretic was given with a fair result.

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Physical examination on the admission revealed a fairly well nourished male without marked impairment of general condition. Temperature was 36.8°C, pulse was regular but feeble with the rate of 108 per minute. Blood pressure was 98/78 mm. Hg. Respiration rate was 20 per minute. Slight jaundice was noted at the bulbar conjunctiva. In the upper half of the body, a moderate venous engorgement was observed, but there was no obvious edema. Cardiac dullness extended 2 fingerbreadths to the right from the right sternal border, and the left border extended beyond the anterior axillar line. Apical beat was palpable. Slight systolic murmur was heard at the apex, and an occasional friction rub was audible at the sternal border in the 3rd interspace. Both the 1st and 2nd sounds

Table I. Laboratory Findidgs (1)

			On the admission	During the 2nd period	During the 3rd period
Blood study	Hb (Sahli) (%)		125	128	120
	RBC ($\times 10^4$)		544	576	586
	WBC		6,100	11,500	18,500
	Differential count	Nonseg.	2		8
		Seg.	78		81
		Eos.	2		1
		Mon.	4		3
		Lymph.	14		7
	Prothrombin time		20″ (49%)		
	Hematocrit		47	57~51	49
Erythrocyte sedimentation rate (30′—60′)			0.5—1	0—2	2—5
Urinalysis	Albuminuria		(−)	(−)	(+)
	Sediments (Erythrocyte)		7~8		10~
Blood chemistry	Icterus index		18	18	68
	BSP test (45′)		20%		
	Zn. turbidity test		4.7	5.4	
	Total protein		5.6	6.5	5.6
	A/G ratio		1.53	1.71	1.27
	Chromatography of protein				
	Albumin			55.6%	
	α-globulin			16.2%	
	β-globulin			12.8%	
	γ-globulin			15.4%	
	Alkaline phosphatase			2.4	2.8
	Total cholesterol	(mg./100 ml.)	150		
	NPN	(mg./100 ml.)		83~46	84
	Na	(mEq./L.)	134	154	
	K	(mEq./L.)	3.6	4.8	4.3
	Cl	(mEq./L.)	101		

were slightly diminished in intensity and were not clear. Lung field revealed no remarkable changes. The liver edge was palpable 3 fingerbreadths below the right costal margin with a moderate tenderness. Slight pretibial edema was noted. Neurological examinations were negative.

Table II. Laboratory Findings (2)

Serum Wassermann reaction	(−)
Rose reaction	(±)
C-reactive protein	(±)
Anti-streptolysin O titer	100
Tuberculin reaction	(++)
Virus compl. fixation reactions (Influenza A, B and Adenovirus)	(−)

Laboratory findings were presented in Table I and II. Arm-to-tongue circulation time was 40 seconds. Venous pressure at the forearm was 140 mm. H_2O. Chest X-ray films prior to and on the admission were presented in Fig. 1 and 2,

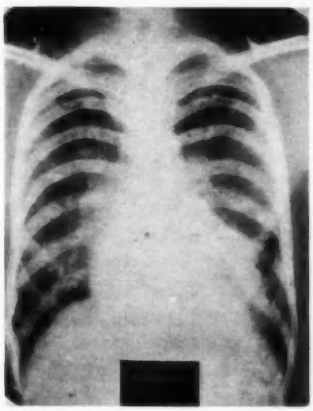


Fig. 1. Chest X-ray film prior to the admission (May 22, 1960).

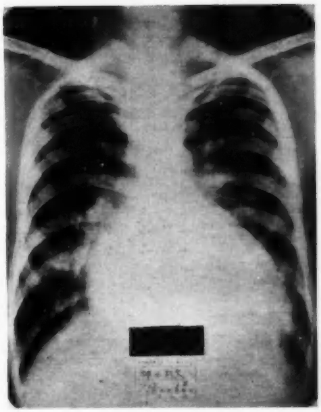


Fig. 2. Chest X-ray film on the admission (July 16, 1960).

respectively. Although slight cardiac enlargement was noted in May (C. Th. R. 65), a remarkable increase in the cardiac size was observed in July, at the time of admission (C. Th. R. 71). Cardiac silhouette was round in PA film and right and left anterior oblique films showed a similar configuration. Roentgen-kymogram of the heart (Fig. 3) showed a remarkably diminished contractibility,

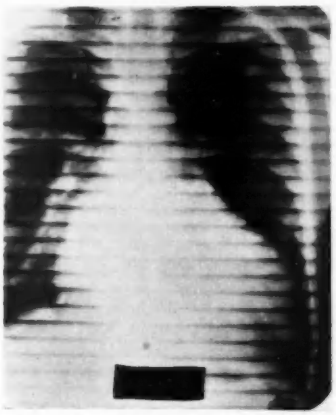


Fig. 3. Roentgen-kymogram (July 20, 1960)

especially in the left ventricular segment. Electrocardiograms (on May 16 in Fig. 4, on admission in Fig. 5) revealed an atrial overload and nonspecific

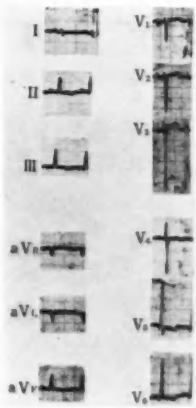


Fig. 4. Electrocardiogram prior to the admission (May 16, 1960).

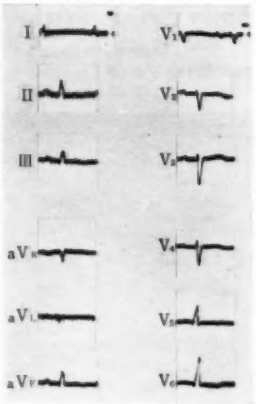
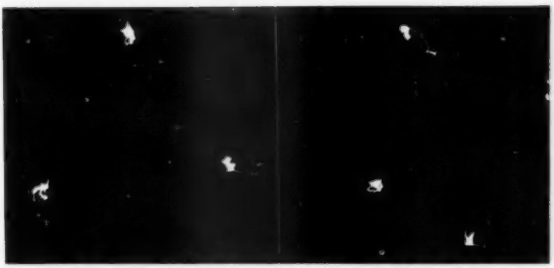


Fig. 5. Electrocardiogram on the admission (July 16, 1960).

myocardial damage, namely the abnormal P-waves, a low voltage and notching of QRS-complexes, depression of ST-segment and flattening or inversion of T-wave in several leads. Vectorcardiogram (Fig. 6) was also suggestive of partial defect of electromotive force, especially in the septal and anterolateral portions. Phonocardiogram (Fig. 7) showed slight systolic murmur in an inspiration over the apex, splitting of the 1st and 2nd sounds over the 3rd left interspace.

The clinical course was presented in Fig. 8, and some laboratory data were tabulated in Table I. In the 1st period of the clinical course, the pretibial edema was subsided with the medication, the patient was in nearly good condi-



(Grishman method) (Frank method)

Fig. 6. Vectorcardiogram (July 20)

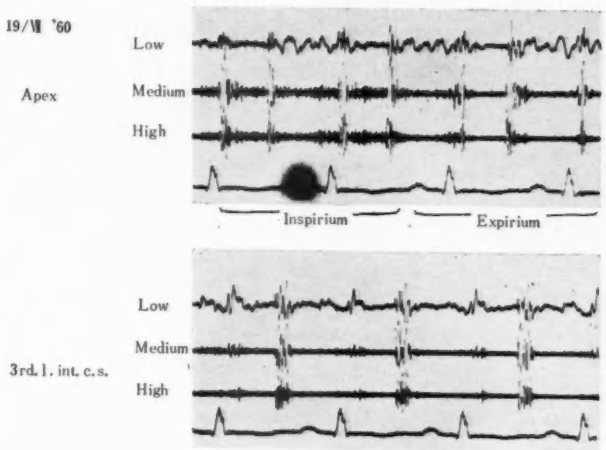


Fig. 7. Phonocardiogram (July 19)

tion. The 2nd period of his clinical course began when he developed dyspnea with intensive perspiration with coldness of extremities during the night of July 21. In the following morning, an elevation of venous pressure and hematocrit value was discovered, but neither hypokalemia nor marked arterial hypotension was present. Slight cyanosis appeared in the afternoon. Because of these symptoms treatment was given such as oxygen inhalation, an administration of cardiotonicum and Ringer's solution etc. However, despite a temporary improvement of general condition several attacks of nonexertional dyspnea with marked perspiration and mental turbulence occurred. Tachycardia and tachypnea were gradually increased, pulsus alternans and gallop rhythm were occasionally recognized. Tubular breath sounds and moist râles of moderate degree became audible over the entire lung field especially posteriorly. The patient had hematemesis on July 31 unexpectedly. Despite an extensive treatment, his conditions deteriorated thereafter (in the 3rd period) with elevated temperature, increased tachycardia, repeated hemoptysis and an increased edema and jaundice.

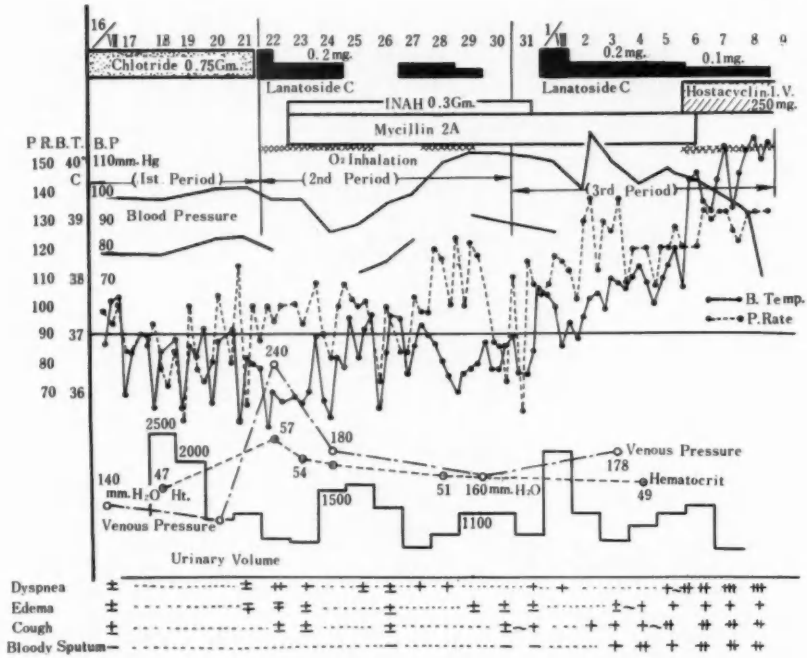
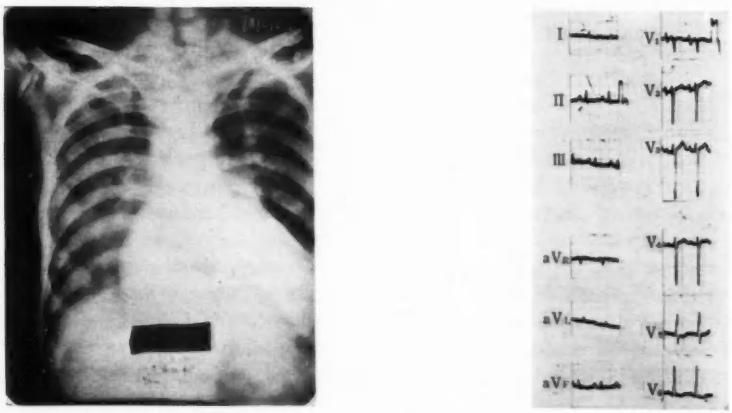


Fig. 8. Clinical course after the admission. Changes in body temperature, pulse rate, blood pressure, venous pressure, hematocrit value, urinary volume, several symptoms, and some medications are shown.



(a) (b)

Fig. 9. Chest X-ray film (recumbent position) (a) and electrocardiogram (b) one day before the death (Aug. 8).

On Aug. 6, the dyspnea and cough became worse and the temperature rose to 40°C. The patient died on Aug. 9, the 25th hospital day, 4 months after the onset of the symptoms.

Chest X-ray film one day before the death revealed a widespread shadow in the right lung, but no essential alterations were observed in the electrocardiogram (Fig. 9).

Autopsy findings: Body height 159 cm., weight 37 Kg.

The heart exhibited globular form, weighing 450 Gm. The pericardial sac containing 70 ml. of brownish serous fluid revealed no signs of inflammation. All chambers of the heart showed marked dilatation but slight hypertrophy. The left and right ventricular walls measured 1.3 cm. and 0.4 cm. in thickness respectively. The main branches of the coronary arteries showed normal distributions and were patent throughout without any atheromatous plaque.

In the left ventricle, 2 red thrombi adhered to the endocardium of the inflow tract, one of which measured 6×3 cm. on the anterolateral region, and the other 6×2 cm. on the apicodorsal region of the ventricle (Fig. 10). These 2 large thrombi

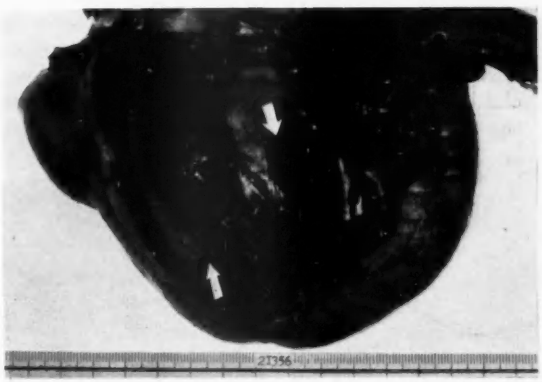


Fig. 10. Two large thrombi in the markedly dilated left ventricle (arrow mark). Endomyocardial fibrosis beneath the thrombi.

permeated extensively to interstices of the trabeculae carnae, and were partially organized. They showed irregular surfaces and were easily friable. The mural endocardium of outflow tract in the left ventricle was almost intact, and there was a considerably sharp demarcation against the endocardium of inflow tract on which ash-colored fibrous thickening was observed, especially in the vicinity of the thrombi. The myocardium of the left ventricle was conspicuously flabby and coarse. About inner one half of myocardial fibrosis was found beneath the endocardial fibrosis of the inflow tract. This finding was particularly remarkable beneath the thrombi. The dilated left atrium revealed an irregular widespread endocardial thickening without any thrombus formation.

The right ventricle was conspicuously dilated with slight and localized thickening of the endocardium. The right atrium had a 1.5 cm. sized red thrombus on the anterior wall and an irregular endocardial fibrosis in the vicinity of the thrombus.

The valves were almost intact except a slight nonspecific thickening at the margin of mitral leaflets and posterior leaflet of tricuspid valve. No congenital anomalies of cardiovascular system were detected.

Pathological changes other than that in the heart were; hemorrhagic infarctions in the right lung, passive congestion of viscera, small ulcers of the esophagus, and petechial bleedings in the stomach. In the right lung, multiple fresh hemorrhagic infarctions were disseminated throughout and were accompanied by an intensive congestion. The size of these infarctions varied from the size of hen's egg to walnut in both upper and lower lobes, and there were cherry-sized multiple infarctions in the middle lobe. No other infarction was found elsewhere in the body including the left lung.

Histological findings: The large red thrombi on the parietal endocardium in the left ventricle showed an organizing process with an infiltration of a few lymphocytes, plasma cells, macrophages laden with hemosiderin, and fibroblasts. Pathogenesis of the endocardial fibrosis in the vicinity of the thrombus was considered to be thrombogenic. Despite of a marked collagenosis of the endocardium, an almost normal elastic layer and subendocardial connective tissue were observed (Fig. 11). The fibrosis appeared partly myxomatous and relatively rich in cellularity. As a whole, fibroelastosis was not found in the endocardial fibrosis, however, a slight increase in delicate elastic layer was disclosed at a limited part where the elastic fibers splitted (Fig. 12). The myocardium of the left

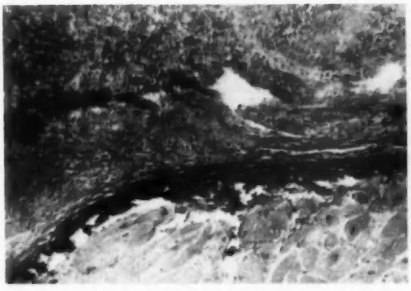


Fig. 11. Organizing endocardial thrombus and almost normal elastic layer and subendocardial connective tissue layer.
50×, Elastica van Gieson's stain.

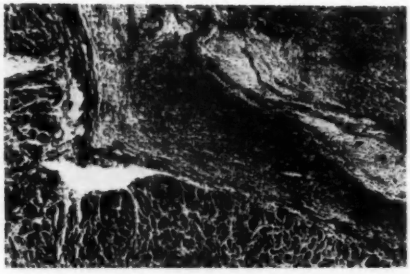


Fig. 12. Increase in delicate elastic fibers at a limited part where the elastic layer splitted.
20×, Elastica van Gieson's stain.

ventricle had a numerous, irregular and disseminated focuses of fibrosis (Fig. 13). It was found that in the subendocardial fibrosis there were dilated blood vessels especially the thebesian veins, myocytes laden with fatty droplets, marked edema, but no signs of inflammation.

The coronary arteries in the myocardium were dilated, and had neither sclerotic changes nor verrucous angitis. The nuclei of muscle fibers were commonly square shaped, pycnotic and hyperchromatic. The swollen muscle fibers appeared edematous and showed a marked vacuolization of sarcoplasmas (Fig. 14)

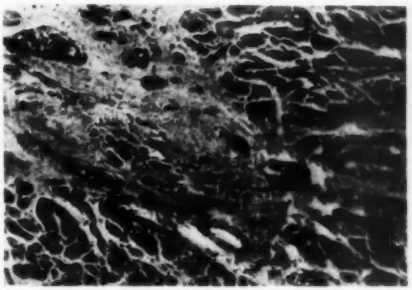


Fig. 13. Focal myocardial fibrosis.
50×, Hematoxylin-eosin stain.

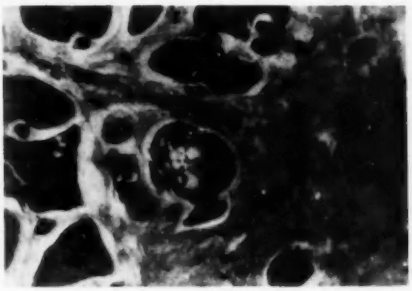


Fig. 14. Vacuolization of the muscle fibers and pericellular fibrosis.
200×, Hematoxylin-eosin stain.

but no basophilic degeneration. Interstitial and interfibrillary edema were also marked. The valvular leaflets were almost normal but slightly edematous. Histological findings of the right ventricle and the both atria exhibited almost the same findings but slight in degree than those in the left ventricle.

Microscopical changes other than those in the heart consisted of passive congestion and edema of the viscera, such as brown induration of the lungs with hemorrhagic infarctions in the right lung, central congestion and fatty degeneration of the liver cells, and turbid swelling of the kidneys.

Comment

The clinical and pathological features of endomyocardial fibrosis have been described and reviewed in detail in several reports from Uganda, by Davies[2)-5)] and others.[1),3),4)] The essential pathological lesion is a fibrosis of the endocardium of the ventricle, with frequently superimposed thrombus formation. The pericardium itself shows no abnormality, and the atrioventricular valves are frequently involved.[4),5)]

Clinical pictures of the congestive heart failure due to endomyocarcial fibrosis is quite similar to those due to constrictive pericarditis,[1),3),6)] and sometimes it may resemble the picture of congestive failure due to common valvular heart disease[4)] when a lesion affects mitral or tricuspid valves.[2),4)] The cardiac failure is commonly progressive and refractory to the treatment.

In the present case, the clinical picture on the admission was considered to be quite similar to that of pericarditis because of a rounded cardiac enlargement with markedly diminished contractibility, congestions without sufficient cardiac murmurs, low pulse pressure, and occasionally audible friction rub, etc. However, the presence of pericardial effusion was discerned, because of a paradoxically palpable apical beat in addition to the finding of a constant configuration of the cardiac silhouette in the

X-ray film in spite of the alteration of body position, etc. It was considered clinically that the disease might be due to an obscure cardiopathy, such as endocardial sclerosis.

In the pathological view point, this case was considered to be very similar to endomyocardial fibrosis described by Davies, in the following points; 1) endocardial fibrosis confined to the inflow tract, 2) practically no increase of the elastic fibers in the thickened endocardium, 3) no inflammatory signs either in the endocardium or myocardium, 4) no angitis in the myocardium, 5) vacuolization of muscle fibers with an intensive myocardial fibrosis of the inner half layer of the ventricular wall.

There were, however, several points of dissemilarity to Davies' cases; 1) presence of markedly dilated left ventricle, 2) friable endocardial thrombosis resulting in pulmonary infarctions, 3) presence of a normal endocardial structure at the deeper layer of the endocardial fibrosis, 4) absence of hyalinization in the endocardial fibrosis.

In conclusion, a diagnosis of an endomyocardial fibrosis was made in an obscure heart disease after studying the clinical and pathological features since other diseases which involve endomyocardium, such as Becker's disease,[7] Löffler's endocarditis parietalis fibroplastica,[8),9),10] endocardial fibroelastosis,[11),12] nutritional heart disease in Africa,[13),14] endocardial fibrosis, [15),16] or beri-beri heart disease[17] had distinctly different features from the present case.

An overwhelming majority in geographical incidence of endomyocardial fibrosis has been found at Uganda in Africa, but there have been several reports from other districts such as Kenya,[6] South and West Africa, South India, Ceylon,[18] Sudan,[16] Malaya, Hawaii and United States, etc. In Japan, it has not been reported in so far as the authors' recognition.

Summary

A 30-year-old male, an autopsied case of endomyocardial fibrosis was reported. The patient died about 4 months after the onset of symptoms due to a progressive cardiac failure complicating infarctions in the right lung. The autopsy findings of the heart revealed; a marked dilatation of all chambers, an intensive endocardial fibrosis of inflow tract with mural thrombi in the left ventricle and right atrium, fibrosis of inner half layer of myocardium beneath the endocardial fibrosis, etc. There were no congenital anomalies, valvular changes, coronary sclerosis, or pericarditis, etc. No signs of inflammation were detected in the endocardium, myocardium or blood vessels.

This case is the first report of endomyocardial fibrosis in Japan.

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